# The health and economic burden of multimorbidity in Australia

By

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## Declaration of originality

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## Statement of ethical conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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# Statement of authorship

This thesis includes papers for which Lili Wang (LLW) was not the sole author. LLW conceptualised the papers, analysed the data and wrote the manuscripts, and where relevant. The contributions of LLW and co-authors are detailed below.

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## Abstract

**Background:** Multimorbidity is a major challenge facing governments and health-care systems worldwide due to increasing prevalence globally, the high consumption of resources and the implications for health care. Multimorbidity is commonly defined through a simple count of health conditions, using a cut-off of 2 or more or 3 or more conditions. There is also increasing interest in statistical approaches to definition. No consensus of the definition of multimorbidity yet exists, which hinders comparisons between studies and advancement of the field. The vast majority of studies have been conducted in clinical or age-restricted populations, with few representative population studies available. No studies have been performed to examine the association of multimorbidity and health status using different definitions of multimorbidity. Moreover, multimorbidity and its effect on productivity in the Australian working population, the health of which is central to the economic strength of the country, has not been well studied.

**Aims:** The primary aim of this thesis was to assess the associations of multimorbidity with quality of life, health care service use, productivity losses and the related financial burden, particularly in the working population. Three different cross-sectional data sets were interrogated and a systematic review was conducted. A secondary aim was to assess to what extent current large national prevalence surveys in Australia are fit for purpose in surveillance of multimorbidity and its correlates.

**Methods:** The Australian National Survey of Mental Health and Wellbeing 2007 were used in Study I (Chapter 3). The health-related quality of life (HRQoL) scores were measured using the Assessment of Quality of Life (AQoL-4D) instrument. The simple count (2+ & 3+ conditions) and hierarchical cluster methods were used to define/identify clusters of multimorbidity. Linear regression was used to assess the associations between HRQoL and multimorbidity as defined by the different methods. The data derived from the Australian National Health Survey (NHS) 2011-12 was used in Study II (Chapter 4) to understand how Australian employees use health

service for a single disease when suffering from multimorbidity. The health service use was reported for each health condition in the NHS and thus it was impossible to tabulate service use by the disorder count. However, the NHS 2011-12 was a large population-based Australian data source including the health status, employment status and health service use of over 10 thousand working adults. This data was the latest available in Australia when we conducted this study. The employee self-reported 2013 data derived from the partnering Healthy@Work (pH@W) survey of all state government employees in Tasmania (including 3,228 Australian employees) was used in Study III (Chapter 5) to assess the associations of multimorbidity on health-related productivity loss by sex as these associations influenced by sex were inconsistent. Data were weighted for non-response. Measures of absenteeism, presenteeism and lost productive time (LPT) were obtained from employees' self-reported data over a 28-day period. Analyses were stratified by sex, and negative binomial models were used to estimate the associations between multimorbidity and the lost productivity time. In Chapter 4 and 5, multimorbidity was defined as the co-occurrence of 2+ chronic conditions out of a pre-specified list depending on the different surveys used. Study IV (Chapter 6) was a systematic review of costs-of-illness (COI) studies of multimorbidity registered with Prospero (an international prospective register of systematic reviews). The search strategy combined key words related to multimorbidity, comorbidity and multiple chronic health conditions. The search was restricted to papers written in English and published since 2000 up to October 2016. The inclusion criteria were peer-reviewed cross-sectional, cohorts and modeling COI studies on multimorbidity, whereas the exclusion criterion was studies focusing on an index disease. The review summarized the current state of evidence and evaluated the quality of cost of illness studies of multimorbidity using the British Medical Journal Checklist for authors and peer reviewers of economic submissions.

**Results:** Study I: HRQoL was negatively associated with multimorbidity regardless of the definition of multimorbidity used. Statistically significant clusters were identified through hierarchical cluster analysis and verified by sensitivity analysis. Study II: the prevalence of multimorbidity in the working population was 23.4% using two cut-off count method. Multimorbid employees with arthritis had higher adjusted arthritis-specific GP visit rates compared to employees with arthritis alone.

Similarly, multimorbid employees with CVD had higher adjusted CVD-specific specialist visit rates and CVD-specific other health professional visits than employees with CVD alone. Study III: the positive association of multimorbidity and LPT, and the significant differences in LPT between men and women reporting multimorbidity were identified. Both sexes with multimorbidity were more likely to have greater productivity loss due to absenteeism or presenteeism compared to those without, but female employees with multimorbidity were more likely to have lost productivity days due to presenteeism and absenteeism, compared to their male counterparts. The mean number of total days of health-related lost productive time in the past 4 weeks was 1.2 (SD=2.4) and 1.7 (SD=3.5) for male and female employees with multimorbidity, respectively, compared to 0.6 (SD=2.2) and 0.6 (SD=1.8) for males and females without multimorbidity. Both sexes with multimorbidity were more likely to have greater productivity loss due to absenteeism or presenteeism compared to those without, but female employees with multimorbidity had 40% and 30% more lost days due to absenteeism (PR=1.4, 95% CI 1.1-1.8) and presenteeism (PR=1.3, 95% CI 1.0-1.6), respectively, compared to their male counterparts. However, there were no significant differences in days lost productivity between male employees with multimorbidity versus without multimorbidity. Study IV found that within 26 included articles, the definition used in the 14 studies that clearly defined multimorbidity was limited to the two cut-off count method. The methodology used to derive costs differed markedly among the studies. Average annual costs per person with multimorbidity ranged from $US 49-$US 252,313. Using a two cut-off count method, the ratios of multimorbidity versus non-multimorbidity costs ranged from 2-16 within 17 available studies; while using three cut-off method, the ratios ranged from 2-10 within 12 available studies. Among 10 studies providing a breakdown on costs, the largest proportion for multimorbidity was spent on inpatient or medication costs in non-societal perspective studies, and social care costs from the societal perspective. Costs-of-illness studies of multimorbidity were highly heterogeneous. The economic burden of multimorbidity was heavy for all age groups.

**Conclusions:** These findings confirm multimorbidity as a significant public health issue in the general population, as well as in the workforce. Further, these findings provide three notable contributions. The first major contribution is theoretical, and

refers to the definitions used for multimorbidity. Comparison of definitions shows that the count method is still useful due to its ease of calculation, but consistency is needed on whether a 2-disorder or 3-disorder cut-off is most useful. Hierarchical clustering could be used as a supplementary tool to capture the specific common clusters of multimorbidity. A uniform definition of multimorbidity is needed. The second major contribution is practical. This thesis has quantified the impact of multimorbidity on health care resource consumption in the Australian workforce and on productivity in a large Australia occupational cohort. The heavy economic burden of multimorbidity as shown in the systematic review suggests that multimorbidity will be more and more important in the future, especially with social changes related to delayed retirement. Finally, the results from the currently available datasets we used highlight the fact that the currently available data restrict the further exploration of multimorbidity. Standardisation of chronic disease surveillance methodologies in national prevalence surveys would aid in epidemiological investigation of multimorbidity in the general population.

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# Table of contents

# List of tables

# Table of figures

# List of abbreviations

| | |
|---|---|
| ABS | Australian Bureau of Statistics |
| ACGs | Adjusted Clinical Group case-mix system |
| AQoL-4D | Assessment of Quality-of-Life 4D |
| AIHW | Australian Institute of Health and Welfare |
| BEACH | Bettering the Evaluation and Care of Health |
| BMI | Body Mass Index |
| CAI | Computer-assisted Interview |
| CI | Confidence Interval |
| CIDI | Composite International Diagnostic Interview |
| CIRS | Cumulative Illness Rating Scale |
| COI | Cost-of-illness |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPI | Consumer Price Index |
| CRG | Clinical Risk Groups |
| CURF | Confidentialised Unit Record File |
| CVD | Cardiovascular Disease |
| DSM | Diagnostic and Statistical Manual |
| EED | Economic Evaluation Database |
| GAD | Generalised Anxiety Disorder |
| GP | General Practitioner |
| HEED | Health Economic Evaluations Database |
| HILDA | Household, Income and Labour Dynamics in Australia |
| HIV | Human Immunodeficiency Virus |
| HPQ | Health and Work Performance questionnaire |
| HRQoL | Health-related Quality of Life |
| HSU | Health Care Service Utilization |
| ICD | International Classification of Diseases |
| IRCMo | International Research Community on Multimorbidity |
| K10 | Kessler 10 Psychological Distress Scale |
| LPT | Lost Productive Time |

| | |
|---|---|
| MDD | Major Depressive Disorder |
| MEPS | Medical Expenditure Panel Survey |
| MM | Multimorbidity |
| NCDs | Non-communicable Diseases |
| NHMRC | National Health and Medical Research Council |
| NHPA | Australian National Health Priority Area |
| NHS | National Health Survey |
| NICE | National Institute for Health Care Excellence |
| NRFUS | Non-Response Follow-Up Study |
| NSMHWB | National Survey of Mental Health and Wellbeing |
| OOP | Out-of-pocket |
| PR | Prevalence Ratio |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO | Prospective Register of Systematic Reviews |
| PSU | Population Sampling Unit |
| RADL | Remote Access Data Laboratory |
| RR | Risk Ratio |
| Rx-MG | Rx-defined Morbidity Groups |
| SD | Standard Deviation |
| SE | Standard Error |
| WHO | World Health Organisation |

# Publications

## Publications directly arising from the work described in this thesis

Chapter 3:

**Wang LL**, Palmer AJ, Cocker F, Sanderson K. Multimorbidity and health-related quality of life (HRQoL) in a nationally representative population sample: implications of count versus cluster method for defining multimorbidity on HRQoL. Health and Quality of Life Outcomes. 2017, 15(1): 7.

Chapter 4:

**Wang LL**, Palmer AJ, Otahal P, Cocker F, Sanderson K. Multimorbidity and Health Care Service Utilization in the Australian Workforce. Journal of occupational and environmental medicine, 2017, 59(8): 795-802.

Chapter 6:

**Wang LL**, Si L, Cocker F, Palmer AJ, Sanderson K. A systematic review of studies estimating the costs and expenditure associated with multimorbidity. The manuscript has been accepted by Applied Health Economics and Health Policy on 14 Aug 2017. The final publication is available at Springer [DOI: 10.1007/s40258-017-0346-6].

## Manuscript submitted for peer-reviewed journal

Chapter 5:

**Wang LL**, Cocker F, Kilpatrick, M., Otahal P, Si L, Palmer AJ, Sanderson K. The Associations of Multimorbidity with Health-related Productivity Loss in a Large and

Diverse Public Sector Setting: A Cross-Sectional Survey. Under review with Journal of occupational and environmental medicine on 14 August 2017.

## Conference abstract published using the work described in this thesis

**Wang LL**, Palmer AJ, Cocker F, Sanderson K. Multimorbidity and Health Care Service Utilization in the Australian Workforce: Findings from the National Health Survey. Value in Health, Volume 19, Issue 7, November 2016, Pages A808-A809. DOI:10.1016/j.jval.2016.08.717

## Conference presentations using the work described in this thesis

Wang LL, Palmer AJ, Cocker F, Sanderson K. Multimorbidity and Health Care Service Utilization in the Australian Workforce: Findings from the National Health Survey. Pharmacoeconomics and Outcomes Research (ISPOR) 7th Asia-Pacific Conference, 2016, Singapore. Oral presentation.

Wang LL, Palmer AJ, Cocker F, Sanderson K. Multimorbidity and health-related quality of life (HRQoL) in a nationally representative population sample: implications of count versus cluster method for defining multimorbidity on HRQoL. The Population Health Congress 2015, Hobart, Australia. Poster presentation.

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# Chapter 1. Introduction

## 1.1 Preface

This chapter provides a broad overview to my thesis including basic conception of multimorbidity, measures and prevalence of multimorbidity and the impact of multimorbidity on the health care needs and costs to the society. The evidence on what is known about multimorbidity and the impact on the working population is then reviewed. In order to situate the overall research aims of this thesis, Chapter 1 reviews the key literature on how we identified the gaps step by step. More specific reviews of relevant literature are provided in Chapters 3 to 6.

## 1.2 What is multimorbidity?

Nowadays, more and more people with multiple coexisting health conditions is a major challenge facing the governments and health-care systems worldwide. This phenomenon includes not only those individuals with an index disease, which we are familiar with and known as comorbidity, but also those in whom multiple diseases co-exist without an index disease, which was known as multimorbidity. However, these two terms require a clear distinction because of the inappropriately interchangeable use in the literature.

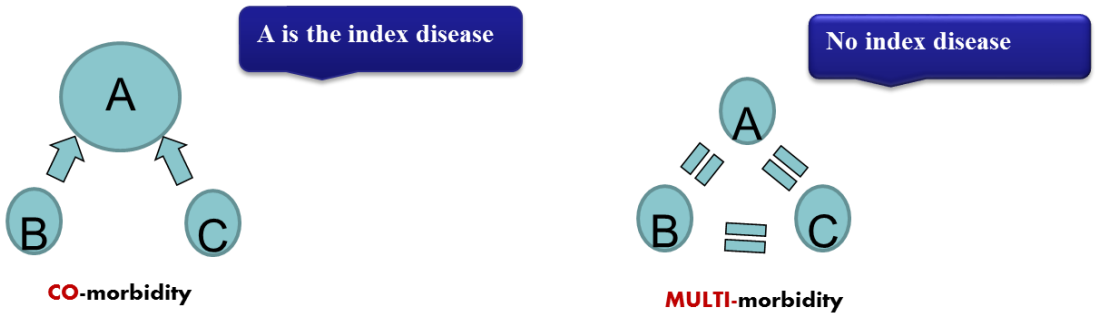
### 1.2.1 Comorbidity & Multimorbidity

Comorbidity and multimorbidity are the terms used most often when referring to the state of having multiple coexisting health conditions [1]. "Comorbidity" is usually defined as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [2]. This definition differs from the newer concept of "multimorbidity", in which several overlapping chronic health conditions are managed as equally-important to patient quality of life and outcomes [3]. Nevertheless, much confusion still exists in the literature, where the terms of multimorbidity and comorbidity have been used interchangeably in studies

on multiple co-existing health conditions [1]. It is thus important to clarify these concepts.

The term of comorbidity was coined by Feinstein in 1970, while multimorbidity first appeared in the German literature, when published and translated by Wittig *et al.* in 1976 [4], and was then used broadly as a term in the medical literature [5]. The definition of comorbidity emphasizes the unique role of one condition in a group. When there is a predominant health condition, triggered secondary health conditions which are caused by this predominant one, may occur during its clinical course [6]. People can easily access healthcare services in this state, as the current health care system is predominantly designed to deliver care for single diseases, and patients can receive relevant treatments for secondary conditions as well during the treatment of the index condition. For instance, a person with diabetes who is affected by the associated retinopathy (comorbidity) can be g appropriately treated for retinopathy based on diabetes guidelines; however, a person with diabetes, cancer and cardiovascular disease (CVD) at the same time (multimorbidity) cannot obtain a completely effective treatment package for all of these three diseases. That is, a framework in which one health condition is considered central may not be useful when considering the optimal care and a health care system for multimorbid people, unless one health condition is dominant in terms of the well-being and health care of one person [6, 7].

**Figure 1-1.** The differences between comorbidity and multimorbidity.




*Suppose there are three health conditions: A, B and C.

Therefore, this thesis focused on two critical components of multimorbidity that are distinct from "comorbidity": "no index disease" and "simultaneous coexistence".

### 1.2.2 Concerns about Multimorbidity

Multimorbidity has drawn more concerns than comorbidity. The first concern pertains to the increasing global prevalence of multimorbidity.

Studies on the prevalence of multimorbidity have been conducted globally and show that multimorbidity is far more prevalent than each single health condition alone [8, 9]. Globally, more than 25% of people on average suffer from multimorbidity [7, 10], and this figure is expected to increase in the coming years [11]. In the general population, the prevalence of multimorbidity has ranged from 13.1% to 71.8% across studies [12] and, the boarder prevalence in the primary care setting ranged from 3.5% [13] to 98.5% [14]. For example, Schram *et al.* pooled data from seven various levels of databases to estimate the prevalence of multimorbidity, which was most prevalent in nursing homes (82%), followed by in the general practitioner registries (56%-66%), general population (56%-71%) and the hospital setting (22%) [15]. In the Netherlands, Uijen *et al.* found that the prevalence of individuals with two or more chronic health conditions increased from 12.3% to 20.5% over two decades, from 1985-2005 [16]. In America, Ward *et al.* found that this prevalence increased from 21.8% in 2001 to 25.5% in 2012 [17, 18]. Although the prevalence of multimorbidity varies depending on the population source as well as the definition and measure of multimorbidity, an increasing prevalence has been clearly observed [19].

Moreover, as the number of health conditions included in the definition increases, the prevalence estimates of multimorbidity also increase [20]. For example, Fortin *et al.* used a list of seven health conditions as well as an open list of conditions and found that compared with the estimates for the list of seven health conditions, the multimorbidity prevalence estimates for the younger age group based on the open list in the practice-based group were approximately 4.3 times and 2 times the estimates of the middle-age group [20].

The second concern regarding multimorbidity is the higher consumption of resources.

A higher number of multimorbid conditions has consistently been shown to be associated with a substantially greater share of resource consumption, including

inpatient services, specialized care, primary care, medications, and even personal time spent on health care, in numerous populations and settings worldwide [21-24]. Approximately two-thirds of the total American health care spending is estimated to be devoted to persons with multimorbidity in the Medicare programme [25]. Furthermore, approximately 58% of patients attending general practice in the United Kingdom have multimorbidity and account for roughly 78% of all consultations [25]. In Australia, the median monthly time spent on health-related activities was 5-16 hours for those with multimorbidity, and patients with five or more conditions spent up to 5-8 hours per day [24].

The third concern is about the implications of multimorbidity for health care systems.

As a global health challenge, multimorbidity has a significant impact on current health systems, given the higher associated health care needs [25]. Challenges arise for all stakeholders. For people with multimorbidity themselves, they suffer from the effects of multiple illnesses without hope, and many prefer being treated holistically rather than as having a series of disparate diseases. This type of person-focussed approach [7] is likely to produce greater gains in self-management and in subsequent improved health and quality of life outcomes [7]. However, health care providers struggle to meet the complex needs of people with multimorbidity and have a sense of powerlessness and frustration, as the guidelines and professional training are largely specific to single-diseases [26]. Moreover, the effects of single diseases are not simply summed within individuals [21]. For governments and society, they have substantial investments in caring for multimorbid conditions with far fewer gains.

### 1.2.3 The absence of uniform way of defining multimorbidity

Although multimorbidity has increasingly becoming the most prevalent "chronic condition" and not the exception [26], effectively and efficiently managing multimorbidity, appropriately allocating the related health resources, and improving quality of life remains an unrealized goal in routine care. A major obstacle to better understanding multimorbidity and providing cost-effective treatment is the lack of consensus regarding how to measure multimorbidity.

At its simplest, multimorbidity is defined as the presence of multiple co-occurring chronic health conditions without an index disease in a given person [27]. Based on this basic definition, four or more health conditions and 1,631 different criteria have been used in the medical literature to identify multimorbidity. Multimorbidity as been investigated within three general categories: i) the number of chronic health conditions (count-based method), ii) the cluster of chronic health conditions (cluster-based method) [28, 29], and iii) questionnaire-based methods. The first one is generally used because of its user-friendly nature and lack of technical requirements, while the second definition is statistically complex; finally, the last definition requires a pre-designed questionnaire that addresses "multimorbidity" in the first place. More details of the differences between these three methods are discussed in the following sections.

Count methods

Although the number-based count method is used widely, recent systematic reviews have raised some specific issues about this approach [12, 30]. The cut-off value, which means the minimum number of co-existing chronic conditions one individual should have to determine the presence of multimorbidity, is the first issue [21]. Different cut-off values have been used [14, 30-32]. For example, Harrison *et al.* reported that in populations with a broader age scope, the two-condition cut-off approach was more appropriate, whereas the three-condition cut-off approach was more appropriate to elderly populations [31]. Furthermore, the two-condition cut-off is recommended when a limited number of pre-specified chronic health conditions are included in the definition of multimorbidity, whereas the three-condition cut-off requires more chronic health conditions to be included [31]. However, all cut-off values should be used with caution, particularly because the number of health conditions in the current studies varies, largely due to data availability; furthermore, the majority of papers did not provide clear reasons for the criteria of included health conditions [12, 30]. Most commonly, they simply chose the health conditions with a high impact or high prevalence [30].

Whether to group multiple health conditions affecting the same body organs into one category or to consider them individually is also controversial. For example, for

myocardial infarction and chronic ischaemic heart disease [30], the prevalence of multimorbidity would clearly be higher when they are considered two conditions rather than only one (CVD). The subsequent health outcomes measure would differ as well [33]. Defining multimorbidity by organ systems may be helpful for reducing health care utilization, as different health conditions in the same organs could be treated by the same health professional.

However, determining whether to group conditions depends on the number and the approach used to access health conditions in the pre-specified lists outlined in surveys. The lack of data regarding precise multimorbid conditions could result in difficulties capturing multimorbidity. More research is thus needed to better understand multimorbidity.

Cluster-based methods

The count methods, which results in all the possible clusters of health conditions, prompted the development of cluster-based methods to identify specific clusters of multimorbidity [34-36]. The main ways by which multiple chronic health conditions can be clustered in an individual are by chance, by selection bias and by causal associations [6]. Two health conditions can coexist simply by chance. Assuming that there is a population in which 4% have type-2 diabetes and 5% have eczema, by chance alone, 0.2% (=4%*5%) of this population would have both conditions [6]. Selection bias occurs due to study design. For example, Berkson *et al.* observed a higher prevalence of clusters of conditions in persons seeking care than in the general population [37], as those accessing health care were more likely to acquire additional diagnoses. Using community samples or population-based data rather than including only patients is an effective approach to preventing this type of bias. Finally, causal associations are more likely to refer to "comorbidity", which is discussed in section 1.2.1 and is not within the scope of multimorbidity and thus will not be discussed further.

The statistical methods used to capture clusters of conditions have also been explored. For example, Cornell et al. used hierarchical clustering analysis [38], Schafer et al. and Prados-Torres et al. performed factor analysis [34, 39], and Islam et al. adopted two other

approaches: principal component analysis and latent class analysis [36]. These studies showed that identifying common clusters of co-occurring health conditions could improve clinician understanding and, to some extent, help develop better practice guidelines for multimorbidity [24, 36, 40, 41]. Some clusters are particularly problematic for both patients and clinicians. For example, clusters of respiratory/cardiac body system morbidities have a strong synergistic negative interaction [42]. The cluster of musculoskeletal health conditions with vascular or upper gastrointestinal symptoms may result in the use of non-steroidal anti-inflammatory agents, increasing the mortality of the other two conditions, particularly in the elderly [43]. The guides for single conditions rarely have taken these issues into account.

Moreover, big differences in the nature of multimorbidity in the different study settings have been identified. Clusters of heart diseases/hypertension/osteoarthritis are predominant in population-based settings, clusters of heart health conditions are most prevalent in the hospital settings, whereas hypertension/diabetes/ osteoarthritis/obesity/lipid metabolism disorders are predominant in the primary healthcare settings. Finally, in the nursing home setting, clusters of dementia, hypertension, and stroke were predominant [15].

Questionnaire-based methods

In addition to the two popular methods mentioned above, researchers have also tried to develop tools to better understand and identify multimorbidity. Comorbidity can occur separately from multimorbidity, we now know that these two conditions should be distinguished from each other. However, given their connection, some tools referring to comorbidity are often used in attempts to access multimorbidity, such as the Cumulative Illness Rating Scale (CIRS) [14, 44-46] and the Johns Hopkins Adjusted Clinical Group case-mix system (ACGs) [47, 48]. The advantage of these tools is that they account for the "severity" of conditions [12]. One disadvantage is the limited space on questionnaires and the reduced response rate due to the additional burden of completing questionnaires [31]. Additionally, the original survey designs require additional mapping of diagnoses from the classification system in which the health records were documented [31]. That is, it is impossible to access these tools if the survey does not incorporate them, particularly if multimorbidity is not currently included in

the regular content of national health surveys. Even in those few available surveys, the target populations are specific, such as in the Bettering the Evaluation and Care of Health (BEACH) programme, which focused on primary health care patients.

Other than the direct quantitative methods used to identify multimorbidity, some studies have also proposed proxy measures in primary care, such as the number of prescribed drugs [49]. These researchers have suggested that this measure could be a potential simple predictor of multimorbidity [50]. However, there is insufficient evidence and the systematic reviews on existing multimorbidity-related methods emphasize the heterogeneity in the current studies [30, 51]. The selection of different methods depends on the type of available data and which is most appropriate according to each study's outcome of interest. Combining different methods in the same study can lead to a better understanding of multimorbidity [51].

A list of included health conditions

The lists of health conditions included in different studies on multimorbidity vary greatly. Some authors have limited their investigations to a short list of conditions of particular relevance to their setting. Others have included all possible health conditions experienced by the individuals. Not surprisingly, the more health conditions that are included, the higher the probability of detecting multimorbidity.

According to the World Health Organization (WHO), multimorbidity is determined by non-communicable diseases (NCDs), which are not passed from person to person [52]. Fortin *et al.* suggested that the most prevalent chronic health conditions with a high impact or burden on a given population should be included in these definitions. Other than non-communicable chronic conditions, chronic but communicable conditions have also been included in some previous studies, including human immunodeficiency virus (HIV) [53] and hepatitis [54]. Moreover, acute conditions are unlikely to be considered in multimorbidity studies, as they may only temporarily influence health status [31] and may not be relevant to long-term health care planning.

In summary, multimorbidity is a state experienced by multimorbid people rather than a medical diagnosis. Although a detailed list would be impossible for all communities,

a list of the most prevalent chronic health conditions with a high impact or burden in a given population would provide a good compromise [12]. Moreover, for the purposes of research and reporting, we should agree on a definition that is measurable, comparable and conceptually sound, as the number and types of health conditions selected and their grouping greatly affect any related estimates.

Different definitions, however, may produce different associations of multimorbidity with health outcomes; these definitions were adopted in isolation before and are hardly comparable due to the variance in settings between the different studies. Therefore, a rigorous evaluation of methods designed to capture variations in the different definitions of multimorbidity and their effects on health status at the population-level is warranted, as the lack of studies examining the association of multimorbidity with health status using different definitions of multimorbidity hinders comparisons and further explorations of multimorbidity-related studies. This is the major challenge we are facing and the **first gap** we identified in this thesis.

## 1.3 Multimorbidity & health-related outcomes

Despite the absence of a uniform method of defining multimorbidity, qualitative work has established that in general, the state of "multimorbidity" is associated with poorer outcomes for multimorbid people. The following sections provide more details about these associations.

### 1.3.1 Multimorbidity & health-related quality of life

Health-related quality of life (HRQoL) is a subjective outcome measure with a multidimensional perspective that is increasingly being used to capture the holistic health status of people with chronic diseases [55]. Although previous studies have shown that HRQoL scores generally decrease with an increasing number of co-occurring chronic health conditions [42, 56, 57], some specific clusters of multimorbidity are more strongly associated with poor HRQoL than others, such as clusters between mental and physical conditions [58]. The combined associations of co-occurring chronic health conditions with HRQoL have received some attention [59-62], and knowledge of

clusters that potentially have a greater impact on HRQoL may help map the population burden of multimorbidity and can inform health planning.

In the literature, there are three main approaches to identifying clusters of multimorbidity: the most prevalent clusters in a given population, clusters of physical and mental disorders and statistical cluster-based methods. The most prevalent clusters in a given population are not necessarily the clusters with the greatest burden. For example, the cluster of diabetes and acid peptic illness was the most costly pair of chronic diseases (excluding psychosis) in an American Medicaid sample but was only present in 30/41,159 people; by contrast, the cluster of hypertension and diabetes was approximately 10 times (310/41,159) as prevalent as the cluster of diabetes and acid peptic illness but was the third least expensive [63]. Clusters of physical and mental disorders are normally of interest in studies focusing on mental disorders, as the clustering may produce a significantly different association of physical disorders with health outcomes. To capture common clusters of multimorbidity with statistical methods, researchers have used cluster-based methods, such as cluster analysis [64, 65], factor analysis [34, 66] and hierarchical analysis [38]. The different methods use different mechanisms to identify clusters, such as, cluster analysis use distance measures, whereas factor analysis and principal component analysis use correlations. In most studies, investigators have used only a simple list of health conditions to detect the clusters in patients, and this list provides very incomplete information that is quite narrow in scope for presenting the association between multimorbidity and HRQoL. However, little is known about the associations between multimorbidity and HRQoL using various methods of defining multimorbidity, as there is no consensus definition.

### 1.3.2 Multimorbidity & healthcare service utilization

People with multimorbidity have complex health care needs compared to those with a single health condition, and they are at risk of insufficient care and adverse treatment effects, such as adverse drug events caused by polypharmacy [67]. Therefore, meeting the health needs of people with multimorbidity and determining how they use health care is an integral part of routine general practice.

Many studies have found that healthcare service utilization significantly increases with each additional condition [67], yet the rate of increase declines per additional condition [68]. People with multimorbidity have higher overall health service utilization than people with a single condition, including more frequent and longer hospitalizations, readmissions, and physician visits [25, 26, 67, 69-71]. However, healthcare utilization is multifactorial and potentially subject to measurement error [72]. The more health conditions a person experiences, the higher the risk is of measurement error. As health care is still predominantly delivered according to individual diseases [73], it is useful to understand health care utilization patterns for diseases when they are multimorbid versus when they occur individually. Additionally, most studies have focused on higher risk populations, such as patients who frequently use healthcare services and the elderly, who are more likely to present with multimorbidity [74].

Understanding how people use health services for single diseases in the context of multimorbidity is essential to gaining insight into their healthcare demands and reduce the consequences of multimorbidity. Increasing health care utilization has been noticed. For example, in Australia, the average number of GP visits has increased from 4.5 per person in 1987–1988 to 5.6 per person in 2012–2013 [75]. However, we were unable to identify any studies that reported the associations between multimorbidity and disease-specific healthcare utilization, which referred to a series of single-disease evaluations.

### 1.3.3 Multimorbidity & the related economic burden

Regardless of the specific definition of multimorbidity adopted, the prevalence of multimorbidity ranges from 13.1% to 71.8% in the general population [12]. Additionally, a growing body of evidence has indicated an increasing prevalence of multimorbidity [11]. In the Netherlands, Uijen and van de Lisdonk found that the prevalence of people with two or more chronic health conditions increased from 12.3% to 20.5% over two decades, from 1985-2005 [16]. In the United States, Ward found that multimorbidity increased in prevalence from 21.8% in 2001 to 25.5% in 2012 [17, 18].

Although multimorbidity is not a specific disease, strictly speaking, it has increasingly become one of the most problematic "chronic health conditions" [76], not only because of the prevalence but also because of its far-reaching consequences. For example, multimorbidity can have a drastic and lifetime impact on the lives of those affected, as it is unlikely to be cured. Additionally, compared to single health conditions, multimorbidity has been related to poorer HRQoL [77], higher health service utilization [70], and negative occupational consequences [78], such as productivity loss due to presenteeism (e.g., 'continuing to work while sick') and absenteeism. Moreover, healthcare resource consumption is expected to increase not only because of the accumulation of chronic health conditions but also because of the interactions and synergies between health conditions within an individual [79]. Given the concurrent changes in epidemiology, the use of resources and morbidity-related costs of multimorbid conditions are likely to have undergone enormous changes as well.

Cost-of-illness (COI) studies have provided valuable information for modelling the costs of chronic conditions and have been performed to evaluate the costs of multimorbidity. However, there is no summary evidence of the economic burden of multimorbidity, especially given the lack of a uniform definition and measurement method. Therefore, a systematic review of studies on the costs of multimorbidity that analyses the different methods used, summarizes the findings on the economic impact of multimorbidity and evaluates the quality of the included COI studies, particularly examining how the costs differ with various definitions of multimorbidity, is urgently needed.

## 1.4 Managing multimorbidity

As described above, there is well-established evidence highlighting the complexity associated with multimorbidity [28, 80, 81]. Compared with those with single health conditions, people with multimorbidity are more likely to die prematurely, be admitted and stay longer in the hospital [82, 83]. They have poorer HRQoL, have loss of physical functioning and are more likely to experience depression and to receive multiple drugs with subsequent difficulties with adherence [84, 85]. The impact of socioeconomic deprivation is also evident, as onset of multimorbidity occurs 10-15 years earlier in people living in the most deprived areas compared with those living in

the least deprived areas [9]. However, the delivery of health care that is predominantly built around single health conditions may not be appropriate for the people with complex health problems and overlapping healthcare services [14, 67].

From a more pragmatic perspective, few studies to date have investigated the effect of multimorbidity on processes of care and what constitutes "best care" for these patients. Although a systematic review on this topic found that the current interventions have had mixed effects [32]. The continuity of health care for the people with long-term health conditions may lead to lower health care costs, fewer health care service visits and complications [86]. Moreover, because of the high prevalent long-term health conditions, the morbidity and mortality could be reduced substantially with a national-level primary healthcare pathway [87]. Improving the awareness of people's understanding of multimorbidity may have implications for the provision of care and for the design of interventions for multimorbid people with complex needs [88]; however, whether these management approaches suit the situation of multimorbidity remains quite unclear.

There is a significant gap in evidence-based recommendations for people with multimorbidity [89], as the current evidence highlights the lack of a clear theoretical framework that currently guides interventions for multimorbidity [32].

## 1.5 Multimorbidity in the working population

Another major challenge to the improved understanding and management of multimorbidity is the rapid demographic and epidemiological changes that have occurred globally [90, 91]. Although the population of people aged 60 years and over will increase from 600 million in 2000 to 2 billion in 2050 [92], living longer does not necessarily mean living healthier [91]. Much of the burden of death and illness occurring in old age is attributable to chronic conditions, which require long-term care [93]. Nevertheless, one issue is that people cannot afford the costs and have to stay in the workforce to support long-term care, even if they have already reached the retirement age. According to recent Australian data, 23% of the working population aged 40 years and over expected to continue working until they were 70 years old, and this proportion was only 8% ten years ago [94]. Therefore, a challenge with particular

relevance for understanding the burden of multimorbidity is the extended working life for many people.

The health of the workforce is central to a country's economic well-being. With 63.4% of all adults worldwide being in the workforce [95], ageing coupled with increasing the national retirement age [94, 96] has led to more employees with multimorbidity in the workforce [97]. Although the prevalence is naturally higher among people aged 65 years and over [26, 67], around half of the multimorbid population is younger than 65 years [21, 81, 98]. All of the figures shown here illustrate that multimorbidity is not only a problem among older adults but is increasingly affecting younger adults, given the sociodemographic and health changes in the population. This is likely to produce notable effects on a particular segment of the population – working adults.

The multimorbid working population is of concern not only because of their health care costs but also because of **productivity losses**, which are much greater and only occur in the working environment [86]. To date, employers have devoted inadequate attention to health-related productivity loss, as they have only attempted to understand medical and pharmacy spending due to poor employees health [99]. The ways in which employers control or reduce the costs may result in worse clinical health outcomes and facilitate productivity loss and include shifting costs to employees and limiting insurance coverage [100, 101]. The cost of lost productivity from employees who are absent due to sickness (also known as absenteeism) and from present employees who cannot fully engage in work due to illness (also known as presenteeism) is substantial [102-104]. The costs of presenteeism itself is two to three times greater than direct health care costs [102].

This situation has become more complex due to co-existing health conditions [105]. A positive association between the number of chronic health conditions and work performance has been observed. For example, in a multi-employer study that combined claims data from 1,134,281 American, Loeppke *et al.* found that productivity loss increased as the number of health conditions increased and was 1.3 times greater than the costs of direct health care [99]. In another study, Lenneman *et al.* adopted a list of five chronic health conditions to assess their relative contribution to

rates of productivity impairment and concluded that there was significant growth in impairment as the number of health conditions increased [106]. Additionally, studies have focused on the impact of a specific combination of chronic health conditions on lost productivity, but they emphasized the role of mental disorders. For example, Kessler *et al.* conducted a study using nationally representative data from the United States and found that comorbid mental and physical disorders could result in more role impairment than physical disorders without mental disorders [107].

Very little is known about the impact of multimorbidity on the working population and the type of support people need to continue working while also managing multimorbidity. This lack of knowledge represented **the second gap** that we aimed to address though this thesis. This important gap in understanding was recently recognized by the National Institute for Health Care Excellence (NICE) in the UK though a project that aimed to develop a guide for employers and employees on effective and cost-effective approaches to promote and protect the health of workers with long-term conditions and to effectively manage sickness absence associated with these conditions [108]. However, this gap has not been filled thus far.

## 1.6 The Australian context

This thesis was based on data from the Australian population, and thus the multimorbidity-related context in Australia will be introduced.

Australia faces significant fiscal pressure and policy challenges resulting from the increasing prevalence of multimorbidity and the rising economic burden. There have been a number of effects implemented in response to this situation. However, reports from the Australian Institute of Health and Welfare (AIHW) and the Australian Bureau of Statistics (ABS) recommend that further change is needed to ensure the future development of the Australian health system. To establish and maintain a globally competitive and healthy population, all stakeholders such as clinics, policy makers and people with multimorbidity need to better understand the health-related issues caused by multimorbidity. This is particularly important for the working population, as the Australian workforce is rapidly changing.

In March 2016, ABS released a report "6238.0-Retirement and Retirement Intentions". This publication presented information about the retirement status and intentions of Australians aged 45 years and over who had worked at least two weeks and shown more Australians than ever (4 times of the number in 10 years ago) would not retire until 70 years old. A postponed retirement has led to the increased pressure on health care and often been associated with increased health conditions because of aging. To establish and maintain a healthy and productive workforce, a better understanding of the health issues affecting the Australian workforce is needed. This is particularly important for multimorbidity, which predominantly leads to worse health-related outcomes. However, multimorbidity in the Australian working population has not been well studied.

The national health priorities used in the Australian national health surveys conducted by ABS were determined according to the conditions that were prevalent and highly costly in the Australian community. The health conditions used to capture the nationally representative estimates of multimorbidity in this thesis were consistent with the identified Australian national health priority areas. However, the survey was not initially designed to measure multimorbidity, and thus more research is needed to better meet the exact data collection requirements to address the health-related gaps due to multimorbidity. The **third gap** identified in this thesis was whether our current large national prevalence surveys fully measure multimorbidity.

## 1.7 The need for further research

Studies in the field of multimorbidity research should use more consistent definitions of multimorbidity. Additionally, there is a need for more evidence on multimorbidity and HRQoL using different definitions of multimorbidity based on a nationally representative population. Samples at high risk, such as the elderly and those in primary health care, have been accessed in previous studies, yet there is a lack of adequate evidence in the general population, particularly the relatively healthy, but especially in an important group - the working population. Given the considerable evidence on co-morbid physical and mental disorders with an index mental disorder and of the high effects of mental disorders on reducing health outcomes, more studies

are needed that explore the relationship between co-occurring physical and mental disorders without an index disease and a range of health outcomes.

## 1.8 How this thesis addresses the identified gaps

In sum, the first identified gap was that "no studies have examined the association of multimorbidity with health status using different definitions of multimorbidity"; the second identified gap was the lack of knowledge regarding whether "multimorbidity is an issue in the Australian workforce". Therefore, to address the identified gaps, the primary aim of this thesis was to address the gaps in knowledge regarding the associations of multimorbidity with quality of life, health care service use, productivity losses and the related financial burdens, particularly in the working population.

These gaps in knowledge were addressed using three different large samples of Australians. These samples were from the National Survey of Mental Health and Wellbeing (NSMHW), Confidentialised Unit Record Files, 2007; the National Health Survey (NHS) 2011-13 and partnering Healthy@Work 2013. The first two datasets are representative of the Australian population and therefore allowed us to answer the question of whether our current large national prevalence surveys are able to appropriately measure multimorbidity and whether they need improvement. This was the third gap we identified and the secondary aim of the thesis we wanted to achieve.

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# Chapter 2. Methods

This chapter provides an overview of the data sources used in analyses for Chapter 3-5, and illustrates some of the challenges in investigating multimorbidity in community-based (non-clinical) populations.

## 2.1 The National Survey of Mental Health and Wellbeing 2007- Chapter 3

This data source was used in Chapter 3. Given the confidential natural, NSMHWB2007 provided the basic Confidentialised Unit Record File (CURF) on physical media (a CD-ROM) and required me to register as an approved CURF user. Even the purpose of this survey was to obtain information on selected lifetime and one-year mental disorders, it also collected information on demographic and socio-economic characteristics, the HRQoL score and a range of health conditions of concern to the Australian population [1]. This sample therefore considered appropriate to address our study aim, examining the performance of the count-based and cluster-based definitions of multimorbidity on the sociodemographic profile and HRQoL in a general population. Moreover, this survey is still the most current national prevalence survey of mental disorders using a diagnostic interview that Australia has so far. All technical details from the survey have been reported from the following documents: National Survey of Mental Health and Wellbeing, Confidentialised Unit Record Files Technical Manual-4329.0 [2] and National Survey of Mental Health and Wellbeing: Users' Guide, 2007-4327.0 [1].

### 2.1.1 Study Design

Respondents living in private dwellings included in the survey were selected randomly using a stratified, multistage area sample [2]. This made the younger (16-24 years) and older (65-85 years) age groups have a higher chance of selection for interview than their other members in the household from different age group. To ensure the reliability of estimates derived using the NSMHWB, person and household

weights were developed separately [2]. The first step in generating weights was assigning the initial inverse of the probability (weight) of being selected from the survey. The second step was generating the differential probabilities of selection by age to consider the oversampling of younger and older age groups. The last step was calibrating person and household weights separately to ensure the estimates conformed to the estimated distributions of the population rather than to the distribution within the sample itself. This process is referred to as 'benchmarking' and can reduce sampling error and the non-response bias. Moreover, in ABS household surveys, the person and household weights were calibrated to population by state, part of state, age and sex, to project the in-scope persons except for those living in the Australian very remote areas, at 31st October 2007 [2].

### 2.1.2 Data Collection

Trained interviewers conducted face-to-face interviews at selected private dwellings. The average length of the interview was 90 minutes [1]. General characteristics of the household and all the included members, including gender, age, and the relationships between household members were collected from one household member aged more than 16 years on the first face-to-face contact. The same interviewee answered questions about household income and housing tenure, on behalf of other household members. This information was used to identify in-scope individuals who were of the survey and one person aged 16-85 years was randomly selected to be included in the next stage of the survey.

### 2.1.3 Survey Response

Initially 17,352 private dwellings were selected for data collection. This was reduced to 14,805 due to no in-scope resident or the dwellings were vacant, under construction or derelict. Of the eligible dwellings, 40% did not respond fully including 61% full refusals, 27% which did not complete the main questionnaire, and 12% which did not provide enough information or cannot be contacted. Of the remaining eligible dwellings, there were 8,841 fully responding households, representing a lower than expected survey response rate of 60%, which can result in a biased sample and create non-sampling error. Therefore, extensive non-response analyses, including

comparison of population characteristics in the NSMHWB2007 with other data sources and a small sample Non-Response Follow-Up Study (NRFUS), were conducted to evaluate the reliability of the survey estimates. No explicit adjustment, however, was made to the weighting strategy because of the negligible impact of extensive analyses on survey estimates [2].

### 2.1.4 Measuring Multimorbidity

To identify multimorbidity, a pre-specified list of chronic physical conditions and mental disorders was used. Chronic physical conditions were obtained via the chronic conditions module. This module contained a standard checklist to obtain information on the prevalence and recency of Australian National Health Priority Area (NHPA) chronic physical conditions [2]. The information was self-reported by the respondent. Even not verified by a medical practitioner, this is a commonly approach the large prevalence population health surveys adopting to measure the prevalence of chronic conditions worldwide [3-6].

These physical conditions included asthma, cancer, stroke (or the effects of a stroke), gout, rheumatism or arthritis, diabetes or high blood sugar levels, and any other heart or circulatory condition. If a respondent had ever been told by a doctor or nurse that they had one (or more) of these conditions, they were then asked i) if they had received any treatment for the condition/s in the 12 months prior to interview, ii) if their condition/s had lasted for six months or more, and iii) their age the first time they had the condition/s [1].

In the NSMHWB, the included mental disorders had to meet three criteria: i) an expected prevalence of more than 1%, based on the diagnosis of a lifetime disorder with or without symptoms in the 12 months prior to interview; ii) they were able to be diagnosed through the WMH-CIDI 3.0; and iii) they were likely to be identified through a household survey. So the selected mental disorders in this survey were diagnostic and considered to have the highest rates of prevalence in the population and that are able to be identified in an interviewer-based survey.

As a result, Chapter 3, which used NSMHWB data, focused on individuals with multimorbidity being defined from a pre-specified list of chronic conditions. They were asthma, cancer, stroke, heart or circulatory conditions (CVD), gout, rheumatism or arthritis, diabetes or high sugar levels, major depressive disorder (MDD) and anxiety disorder (including agoraphobia, with or without panic disorder, generalized anxiety disorder (GAD) and social phobia).

### 2.1.5 Measuring Health-related Quality-of-Life

The Australian-developed Assessment of Quality-of-Life 4D (AQoL-4D) instrument was used to measure HRQoL. The AQoL-4D was brief, using four dimensions, independent living, relationships, mental health and senses) and 12 items measured how a person's health impacted on their self-care, household tasks, mobility, relationships, isolation, family role, sleeping habits, feelings in general, level of pain or discomfort, and seeing, hearing and communication [7]. As a generic instrument, the weighted scoring of AQoL-4D questionnaire is computed to provide dimension scores and an overall index of health state utility and ranged from −0.04 to 1 [8]. A score of 1.00 indicates the best quality of life equal to perfect health, 0.00 indicates quality of life equal to death, and negative values (0 to −0.04) indicates quality of life worse than death [9].

### 2.1.6 Study Sample

The NSMHWB provided a data set consisting of sample of 8,841 respondents aged 16 to 85 years of age and living in private dwellings [2]. No missing data strategy was needed because of the 2.6% low rate of missing data. The final data set in the regression models consisted of 8,820 respondents.

### 2.1.7 Standard error calculation

Because of the NSMHWB's complex survey design, the standard errors presented in Chapter 3 were calculated and adjusted for non-response to remove over- or under-representation of certain demographics [10] using Jack knife delete-1 replication methods [11], behind which the theory [2] is that, the sampling variance between repeated

samples could be obtained by repeatedly taking random, unbiased sub-samples after accounting for the smaller sample size. Jack-knife replicates, particularly are generated by removing one population-sampling unit (PSU) from the dataset at a time and weighting up the other PSUs from the same stratum to adjust for this removal. Therefore, each replicate provides an unbiased estimate of the population mean, and the variance between the replicate means give an estimate of the in-scope sampling variance.

### 2.1.8 Ethics statement

Ethics approval was not required for the study described in Chapters 3 as the used data that were non-identifiable and conducted in accordance with ABS data release policies.

## 2.2 The 2011-12 National Health Survey-Chapter 4

The data source used in Chapter 4 was derived from NHS which is one of Australia's largest health surveys with the health surveillance purpose, conducted by the ABS every three to six years since 1989. It collected information from a range of chronic health conditions (e.g. cancer) and health care service use (e.g. times of visiting general practitioners) for each collected chronic health conditions, demographic and socio-economic characteristics as well as working status of the respondents. Meanwhile, using the weighting strategy, it produced the generalisable estimates of national workforce rather than the particular groups, such as the small-size company or government employees. The data we used was undertaken in March 2011- March 2012 which was the newest one at the time this study was conducted, and therefore considered appropriate to address the study aim, understanding the patterns of healthcare service utilization in employees with multimorbidity. All technical details from the survey have been reported from the document, Australian Health Survey: Users' Guide, 2011-13, 4363.0.55.001 [6].

### 2.2.1 Study Design

The 2011-12 NHS collected information suing face-to-face interviews from usual residents of private dwellings in urban and rural areas of Australia, and covered approximately 97% of the Australian population [6]. Foreigners intending to stay in Australia for 12 months or more were also in scope. Dwellings included in this survey were selected in each state and territory using a stratified multistage area sample. This area-based selection ensured that the selected sample were representative of the people within the geographic scope of the survey. Similar as in the NSMHWB 2007, separate person and household weights were calculated in the NHS to infer results for the total in-scope Australian population.

Unlike the NSMHWB, the NHS CURF was not provided on physical media but was rather accessed via an online analysis tool. The 2011-12 NHS was the component of the Australian Health Survey in the online form of a TableBuilder dataset and an Expanded CURF, which allows the approved users to analyse the dataset via the Remote Access Data Laboratory (RADL) [6, 12]. The Expanded CURF contains unit records relating to all of the survey respondents. To protect the confidentiality of respondents and minimise the risk of spontaneous recognition, some variables were omitted and some variables had the response categories reduced [6]. The effects of the changes made on data for analysis purposes are considered negligible [6].

### 2.2.2 Data Collection

Trained ABS interviewers collected information using CAI instrument. General characteristics of the household such as the number of usual residents of the dwelling residents, their basic demographic characteristics, and the relationships between those people, were obtained from any responsible adult member of a household. In a household, at least one adult and one child (where applicable) were selected for inclusion. No further information was asked from that household if the dwelling contained only usual residents aged under 18 years [6].

### 2.2.3 Survey Response

21,108 private dwellings were chosen in the sample for the NHS. In cases where a respondent refused to do the survey or there was non-contact due to absence at the

time of the visit, a follow-up letter was sent to that household. A second visit was made to explain the aims and importance of the survey, and to answer any particular concerns of respondents. No further contact was made if they refused to participate at the second visit. Except in the Northern Territory where an additional 53 households were obtained to the sample between December 2011 and March 2012, people missed due to non-contact or refusal were not replaced. However, the number of the actual dwellings reduced to 18,355 due to non-response. Ultimately, there were 15,565 fully or adequately responding households, representing a response rate of 84.8%. No explicit non-response adjustment was made to the weighting strategy in NHS, as the effect of the investigated non-response adjustments to the estimates was negligible [6].

### 2.2.4 Measuring Multimorbidity

A pre-specified list of current and long-term conditions was used to identify multimorbidity. Respondents were asked whether they had been diagnosed with any of these conditions, whether these conditions were current at the time of the survey, which conditions had lasted at least six months, and which they expected to last for at least six months. All the reported conditions were coded into a single list, which was initially developed by the Family Medicine Research Centre at the University of Sydney, in consultation with the ABS [6]. Then it was developed by the ABS based on mapping the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) provided by the Family Medicine Research Centre for NHS. The chronic health conditions used in NHS 2011-12, and used to identify multimorbidity in Chapter 4, were kidney disease, heart and circulatory conditions diabetes mellitus, asthma, cancer, arthritis, osteoporosis and mental health. With the exception of kidney disease, all the other conditions listed are NHPA conditions, defined as of great importance in health policy planning and were specifically asked in individual modules to ensure high-quality detailed results for these conditions. As the interest of this study was disease-specific HSU, the non-multimorbidity group would include those with two chronic health conditions when using three cut-off count method to define multimorbidity, which means the disease-specific HSU may be affected by the co-existing health condition. Therefore, we adopted two cut-off rather than three here.

### 2.2.5 Measuring Health Care Service Utilization

To estimate health care service utilization of the included health conditions, the NHS asked the respondents about the number of times they had seen a GP, specialist etc. These questions were only asked once for each health condition group. That meant when a respondent had two or more health conditions, these HSU questions would refer to all the conditions this respondent having in each question. This approach, therefore, restricted the calculation of total HSU for each respondent due to overlapping.

For each condition group that respondents reported having, they were asked whether they had taken any of the actions from a pre-specified action-list (e.g. visited a GP, visited a clinic as an outpatient) in the last 2 weeks. If respondents had not visited a GP in the last 2 weeks, they were asked whether they had visited a GP in the last 12 months, then reported the number of times they had visited a GP during that time. Similarly, respondents who had not consulted a specialist in the last 2 weeks were asked whether they had done so in the last 12 months and again asked to report how many times they had done so. Only the number of GP and specialist visits in the past 12 months were reported in the NHS 2011-12.

### 2.2.6 Study Sample

The employment related information was collected from individuals aged at least 15 years using a short-form version of the questions used in the ABS Monthly Labour Force Survey [6, 13]. People were assigned to three groups including employed, unemployed and not in the labour force referring to "whether the person had a job in the week prior to interview", "whether those who did not have a job were actively seeking work", and "whether those actively seeking work were available to start work". "Employed" respondents were those reporting that in the previous week they had worked in a job including those had a job but were absent from work during that time. Exclusions were those who usually had no more than one hour work time per week, had unpaid volunteer work arrangements, were away from work due to workers compensation, and were not, or did not know if, they were returning to work for their employer or not.

### 2.2.7 Standard error calculation

Similar as in the NSMHWB, the NHS presented standard errors, which indicates the extent to which an estimate might have varied because only a sample of dwellings was included, due to the complex survey design employed.

### 2.2.8 Ethics statement

Ethics approval was not required for the study described in Chapters 4 either as the used data that were non-identifiable and conducted in accordance with ABS data release policies.

## 2.3 The 2013 partnering Healthy@Work (pH@W)-Chapter 5

This data source made available for study in Chapters 5 though the pH@W project, which was led by the University of Tasmania in partnership with the Tasmanian State Service (TSS) and funded by the National Health and Medical Research Council (NHMRC). The survey collected information from the employees aged 18 years and over on presenteeism, absenteeism, the presence of chronic health conditions as well as demographic and socio-economic characteristics. There was no national prevalence survey collecting both multimorbidity and the measures of absenteeism and presenteeism at one dataset, so even not at the national-level, this data source enabled exploration of the extent to which the lost productivity time is affected by multimorbidity which is a concern in the Australian working population. A large employed sample representative of its source population, however, is required as the next best source of evidence in this area.

### 2.3.1 Study Design

Healthy@Work was a health promotion program designed by the TSS and made available to its entire workforce. It had an organisational-level, settings-based approach to promoting health through the workplace, and aimed to support employee health behaviour change through the provision of workplace health promotion activities. Well-tested and commonly used population health questionnaires were used

where available. The pH@W data were collected in 2010 and 2013 using a repeated cross-sectional design [14-19]. Repeated cross-sectional analyses are useful for providing a snapshot of the key health and work factors for the broader population. They were also deemed appropriate for evaluating large-scale program targeted at an entire defined population. Further, there is evidence of cohort and cross-sectional analyses achieving comparable estimates [20]. There were only approximately 500 same participants responding to both of the surveys, so the primary data used in this study was the 2013 survey of TSS employees supplemented with some demographic and employment-related information sourced from the TSS human resources administrative database.

### 2.3.2 Data Collection

The sampling frame was all employees of the TSS. Each employee was assigned a unique code and assigned to a strata which processed by government agency/department, employment condition (full-time or part-time), and employment category (permanent or fixed-term/casual contracts). Using unique code based on the TSS employees ID numbers, employees invited to participate were selected by random sampling within each stratum. The information sheet, consent form and survey instrument were mailed by a commercial mailing company to either a work or home address of each randomly sample employee inviting them to participate in the survey. The completed survey forms were returned directly in reply-paid envelopes to the researchers in Menzies Institute for Medical Research, University of Tasmania.

Oversampling was performed for a number of reasons. First, in very small agencies there was a risk that data from a limited number of respondents could be identifiable if results were to be reported at an agency level. Second, sufficient respondent numbers were needed from each agency to fulfil reporting obligations to the TSS. Third, this increased the numbers available for appropriate weighting and analysis in each agency and work characteristic stratum.

The 2013 survey data were linked with an extract of TSS human resources administrative data. Each sampled employee was assigned an additional unique

pH@W survey ID. The TSS administrative data were matched to survey respondents using these corresponding IDs.

### 2.3.3 Survey Response

Survey response rates to workplace questionnaires are characteristically moderate to low [21, 22]. Nevertheless, previous research has demonstrated that health risk assessments analogous to the pH@W surveys yield similar estimates of prevalence of health-related and work-related factors across subsamples with different response, even when response percentages are as low as 27% as it was in pH@W (3,228/12,007) [23]. Using a method described by Hofler and colleagues [24] and Seaman and White [25] to address possible bias, the data were weighted in analyses using the inverse of the estimated probability of non-response estimated by logistic regression. In effect, this method uses the data of respondents to additionally represent the data of non-respondents to whom the respondent is comparable in terms of the estimated probability of non-response. Inverse probability weighting thus allows inferences to be drawn for the initially sampled population, similar to if all survey recipients had responded. The probability of nonresponse was estimated using a logistic regression model.

### 2.3.4 Measuring Multimorbidity

Multimorbidity was defined with two cut-off count method from a list of 20 pre-specified health conditions from the World Health Organisation Health and Work Performance questionnaire (WHO-HPQ) [26]. Respondents indicated (yes/no) whether they currently had each of the listed conditions or not, including arthritis or rheumatism, chronic back pain, migraine headaches, other frequent or severe headaches, any other chronic pain, high blood pressure or hypertension, congestive heart failure, coronary heart disease, stomach or intestinal ulcer, irritable bowel disorder, chronic heart burn or gastroesophageal reflux disease, asthma, chronic bronchitis or emphysema, chronic obstructive pulmonary disease, urinary or bladder problems, diabetes, osteoporosis, skin cancer, any other type of cancer and mental disorder. Using the count method, the employees then were assigned to one of five categories based on their total number of chronic conditions.

### 2.3.5 Measuring Health-related Lost Productive Time

Three outcomes absenteeism, presenteeism and total lost productive time (LPT) were examined during the four-week recall period in this study. Presenteeism was defined as "working while ill" while absenteeism was defined as "not attending work when ill" [27]. The lost productive rate due to presenteeism were captained by the percentage on a scale from 0% to 100%. Total LPT was the sum of absenteeism and presenteeism days.

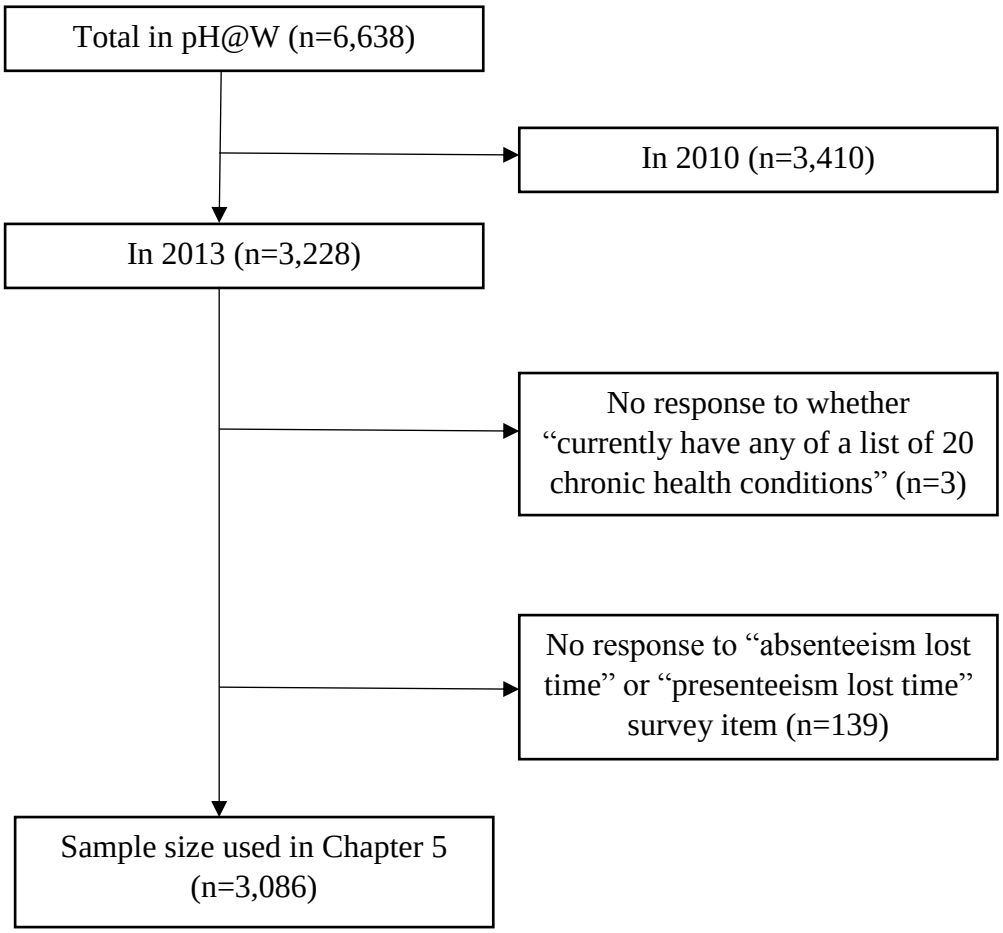
### 2.3.6 Study Sample

In Chapter 5, analyses were conducted using data derived from the pH@W. Derivation of the sample is presented in Figure 2-1.

### 2.3.7 Ethics statement

Ethics approval for the study described in Chapters 5 was obtained from the Human Research Ethics Committee (Tasmania), reference no. H0010501.

**Figure 2-1.** Study sample size described in Chapter 5, derived from the pH@W.



## 2.4 The notes on the used data sources for Chapter 3 to 5

While multimorbidity is more prevalent among older persons and in clinical populations, it also affects younger persons in the general population. A focus on older and/or clinical populations will not capture the full impact of multimorbidity on population health. Thus this thesis has a focus on the community-based population including working populations.

There were also other Australian databases collecting multimorbidity-related information, such as BEACH and the Household, Income and Labour Dynamics in Australia (HILDA). Although BEACH collected data regularly and used a weighted scale to identify multimorbidity, as a primary health care survey it was too narrow in scope for the purposes of this thesis. Most recently, using BEACH Harrison et al. estimated the prevalence of multimorbidity in the Australian general population by weighting the data to match the age-sex distribution of the Australian population [28]. They hypothesised the individuals had no diagnosed chronic conditions if they did not visit a GP in the previous year. But this may underestimate the prevalence of some chronic conditions which did not require health care in a single year. Although the national estimates could be inferred to some extent, a more straightforward analysis is preferred. HILDA is a panel survey which has collected information from 17,000 Australian residents every year since 2001 [29]. HSU coverage in HILDA only includes the number of the doctor visits and hospital admissions for each respondent but no other types of HSU. Moreover, its purpose is providing the linkages between the different life domains rather than focusing on the health surveillance in which we were more interested.

Meanwhile, other kinds of study design are inappropriate for this thesis for following reasons. The randomised control trials are conducted when there is an intervention. The case control studies are the observational studies in which two existing groups differing in study subjects. This design makes the sample potentially unrepresentative of the Australian community [30]. However, given that at present there is little known about exploring the association of multimorbidity with a series of health outcomes in Australian general population, the cross-sectional studies are recognized as an appropriate way when the exposures are the point estimate [31] and provide useful

preliminary data to inform future research when with a large nationally representative sample.

The adopted data sources in this thesis, therefore, appeared to be the best data sources available to address my study aims at the time each study being conducted.

## 2.5 Data analysis

The methods of data analysis for each individual study are reported in each of the relevant chapters of this thesis that details the conduct and results of the studies. All analyses were conducted using STATA (StataCorp, College Station, TX, USA).

## 2.6 References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# Chapter 3. Multimorbidity and health-related quality of life (HRQoL) in a nationally representative population sample: implications of count versus cluster method for defining multimorbidity on HRQoL

## 3.1 Preface

This chapter aims to understand the associations of multimorbidity with HRQoL in the general population, particularly to understand whether the definition of multimorbidity matters and how. This work is important because multimorbidity does not have a universally accepted method of measurement and the implication of these variations has not been explored for HRQoL. Various methods for defining multimorbidity have resulted in poor comparability between studies. To our knowledge, no study has been conducted to examine whether the association between multimorbidity and quality of life varies by methods for defining multimorbidity. The findings of this work provide the first evidence on comparability of the association between multimorbidity and quality of life across different methods for defining multimorbidity, highlighting the urgency of establishing a comprehensive definition for multimorbidity as related to HRQoL. This is also important for developing a target prevention and intervention for improving HRQoL and potentially other health outcomes.

The material presented here has been published in a peer-reviewed journal [1].

## 3.2 Introduction

The presence of multiple chronic conditions, also known as multimorbidity, is in the health care spotlight due to its increasing prevalence, complex management and large economic disease burden [2, 3]. Approximately 25% adults have at least two chronic conditions, and more than half the elderly have three or more conditions simultaneously [4]. Although the prevalence of multimorbidity is higher among adults

aged 65 years and over, more than half of individuals with multimorbidity are younger than 65 years [5, 6], which makes multimorbidity an issue across the lifespan.

HRQoL is a holistic concept that aims to capture a range of health status indices. To date, the impact of multimorbidity on HRQoL has been investigated based on two general categories of multimorbidity: i) the number of chronic conditions (count definition) and ii) the cluster of chronic conditions (cluster definition) [7, 8]. Although HRQoL scores decrease with an increasing number of co-occurring chronic conditions [9], the full impact of multimorbidity on HRQoL is unlikely to be captured by the simple count method [10]. Meanwhile, some specific clusters of multimorbidity, such as the combination of mental and physical conditions [11], have been shown to have a notable effect on HRQoL. However, the impact of the different definitions of multimorbidity on HRQoL in a primary care setting is still unclear [9].

Comparing how the aforementioned categorizations of multimorbidity effect the sociodemographic profile and health status (HRQoL) will provide a conclusive definition of multimorbidity, and consequently, improve health care planning in the context of multimorbidity to match healthcare services with patients' needs. Therefore, using a large, nationally representative dataset, this study examined the performance of the count and cluster definitions of multimorbidity in determining the sociodemographic profile and HRQoL in a general population.

## 3.3 Methods

### 3.3.1 Study design and participants

Our study was a cross-sectional analysis of a nationally representative dataset, the NSMHWB2007, which consisted of a series of face-to-face interviews conducted by the ABS from August to December 2007. Respondents were randomly selected from a stratified, multistage area probability sample of respondents' homes. More methodological information could be found elsewhere. [12] There were 14,805 eligible dwellings out of an initial sample of 17,352 dwellings due to all household members being out of scope or vacant dwellings. Of these, the final data set consisted of 8,841 respondents (60% response rate) aged 16 to 85 years of age and living in private

dwellings. [13] No missing data strategy was used due to the low rate of missing data (2.6%): 21 due to no HRQoL score, 34 due to log-transformed HRQoL score, 180 due to BMI and 6 due to exercise level.

### 3.3.2 Multimorbidity

Multimorbidity was identified from a pre-specified list including the following self-reported conditions that significantly contribute to the global burden of illness and injury [13-15]: asthma, cancer, stroke, CVD, gout, rheumatism or arthritis, diabetes or high sugar levels, MDD and anxiety disorder (including agoraphobia, with or without panic disorder, GAD and social phobia). Each chronic condition was coded as present or absent [13]. The diagnosis of mental disorders was established using the World Mental Health Survey Initiative version of the Composite International Diagnostic Interview version 3.0 (WMH-CIDI 3.0) [15], which is a comprehensive and fully structured diagnostic interview. The timeframe was a diagnosis in the 12 months prior to the interview. Diagnosis of physical chronic conditions was determined from a pre-specified list by whether the respondent had ever been told by a doctor or nurse that they had these conditions, and stroke was assessed using self-reported stroke symptoms [12].

In the count method, multimorbidity was defined as "two or more" chronic conditions occurring at the same time. To test the validation in cut-off of count based method, the definition of multimorbidity "having 3+ chronic conditions at the same time in one individual" (known as complex multimorbidity) [16] was used as well. In the cluster-based method, hierarchical clustering was used to identify the common clusters of multimorbidity as chronic health conditions can co-occur via some sharing underlying genetic, environmental, or behavioural risk factors [17-19]. Assuming N variables, the hierarchical approach initially treated each variable as a cluster before merging the two closest variables into a new cluster. This step was repeated until all variables were merged into one cluster of size N. Jaccard's coefficient was used to calculate the distance of the binary variables (absence or presence of conditions) [17, 20]. The results may vary depending on the different distance calculation methods. Both Ward's and the average linkage methods have been widely used, with the former considered more appropriate for clusters with equal numbers of observations [20] and

the latter recommended to avoid large or tight compact clusters that result from the single linkage and the complete linkage methods [20]. Therefore, we used the average linkage method in this study and used the cluster stopping rule to aid in selecting partitions [21].

### 3.3.3 HRQoL

The AQoL-4D instrument was used to measure quality of life due to its brevity [22], sensitivity and robustness [23]. Four dimensions (independent living, mental health, relationships and senses) consisting of three items each were included for scoring. Then, five new variables, four dimension scores and one overall instrument score, which ranged from -0.04 to 1, were created. A score of 1.00 indicated the best quality of life equal to perfect health, and 0.00 indicated quality of life equal to death, and negative values (0 to -0.04) indicated quality of life worse than death [24].

### 3.3.4 Covariates

Univariate analyses with a 0.25 p-value cut-off were performed to screen the covariates before the second round of screening, involving multivariate analyses. A cut-off of a 10% change in the exposure variable's coefficient estimate in the multivariate model was adopted to identify the "important" variables influencing the association between outcome and exposure. Covariates that remained after these procedures were utilized throughout all subsequent analyses conducted in this study.

The covariates screened in this study included sex, age, registered marital status (married, unmarried), labour force status (employed, unemployed, not in the labour force), area of relative socioeconomic disadvantage (decile 1=most disadvantaged, decile 10=least disadvantaged), body mass index (BMI=self-reported weight/self-reported height$^2$), smoking status (current, ex-smoker, never) and level of exercise (low: <1600 min; moderate: 1600-3200 min, or >3200 min but <2 h of vigorous exercise; high: >3200 min, including ≥2 h of vigorous exercise), which was also used to assess exercise intensity (exercise intensity scores were multiplied by minutes per fortnight) [12].

### 3.3.5 Statistical analyses

Due to the complex survey design used in the NSMHWB2007, a weighting strategy was applied to infer results for the total in-scope population by allocating a 'weight' to each sample unit. The weight was an indication of how many population units were represented by the sample unit [12]. As a result, Jack-knife delete-A-group survey adjustment replication methods were used to calculate the standard errors (SEs) [25]. This process accounted for the stratified multistage sampling framework used in the NSMHWB2007 and adjusted for non-response, which may cause some groups to be over- or under-represented [26]. The theory behind Jack-knife delete-A-group replication methods is that, the sampling variability between repeated samples can be estimated by repeatedly taking random but unbiased sub-samples from the achieved sample and then computing the variance of the sub-samples (after taking the smaller sample size into account). Jack-knife estimation replicates are created by deleting one group at a time, and then weighting the other groups from the same stratum to adjust for the removal. Therefore, each replicate provides an unbiased estimate of the population mean, and the variance of those estimates provides an estimate of the full-sample of the variance. In short, application of these methods ensures the sample is representative of the Australian population, which ensures that subsequent findings are generalizable to Australian adults (n=16,015,000) in 2007 [12].

Frequencies and percentages calculated with jack-knife SEs were used for the descriptive analysis. Hierarchical clustering analysis was used to identify common clusters of multiple chronic conditions. Linear regression models were used to examine the associations between the HRQoL scores and the multimorbidity clusters. In each regression model, the dependent variable was the HRQoL score, and the independent variable was one cluster (present or absent), for example, “whether presenting 2+ chronic conditions” in model-1. The p value for the trend of continuous variables in the linear regression models was given. A log-transformed HRQoL score was used due to its negatively skewed distribution, which resulted in 55 missing values. A two-tailed p-value of $<0.05$ was considered statistically significant. To test the validation in clusters of hierarchical clustering, sensitivity analyses were performed that including factor analysis [27], principal component analysis [28] and K-

means clustering [29], which have been used in previous studies. All analyses were performed using Stata/SE Version 12.1 (StataCorp, College Station, TX, USA).

## 3.4 Results

We analysed data from 8841 respondents which could be generalizable to 16,015,000 Australian adults. The mean age of the study participants was 44 years (SE=0.04). A total of 20.5% (SE=0.6) of the population was obese (BMI >30), 65.2% (SE=0.2) were employed, 72.7% (SE=0.9) reported low levels of exercise, 53% (SE=0.7) were married and 22.3% (SE=0.7) were current smokers. More than half of the respondents (56.7%, SE=0.7) had at least one chronic condition, and 46% had two or more chronic conditions. (Table 1)

Table 2 presents the prevalence of each chronic condition and the percentage of coexistence with other chronic conditions. CVD (21.2%, SE=0.7), arthritis (19.9%, SE=0.6) and asthma (19.6%, SE=0.5) were the three most prevalent conditions. All chronic conditions coexisted with other chronic conditions to various degrees (range from 49% to 91%). Table 3 presents the two common clusters obtained using hierarchical clustering, CVD/arthritis (cluster-1, prevalence=9.2%, SE=0.5) and MDD/anxiety (cluster-2, 4.3%, SE=0.3). In contrast, the prevalence of multimorbidity as defined by the MM2+ and MM3+ count method were 26% (SE=0.6) and 10.1% (SE=0.5), respectively.

The mean ages of the population with MM2+, MM3+, cluster-1 and cluster-2 were 54.6 (SE=0.3), 57.5 (SE=0.6), 63.8 (SE=0.7) and 41.7 (SE=0.7) years, respectively. As expected, prevalence of MM3+ was lower than MM2+ (Table 3), but mean HRQoL was poorer. Interestingly both count methods identified groups with similar socio-demographic characteristics such as female, older, higher BMI, lower education level, less exercise, lower socio-economic status, and not in the labour force. Individuals with MDD/anxiety (cluster-2), which resulting from hierarchical clustering to identify multimorbidity, had the lowest HRQoL scores with the different socio-demographic characteristics comparing to the other hierarchical cluster and count method to identify multimorbidity, such as younger, unemployed, unmarried. (Table 4-5)

Individuals with MDD/anxiety (cluster-2) had HRQoL scores that were 0.38 points (SE=0.02; p<0.01) lower than those without cluster-2. Individuals with any two or more chronic conditions (MM2+) had HRQoL scores that were 0.21 points (SE=0.01; p<0.01) lower than those with no more than one chronic condition. Individuals with any three or more chronic conditions (MM3+) had HRQoL scores that were 0.26 points (SE=0.02; p<0.01) lower than those with no more than two chronic conditions. Individuals with CVD/arthritis (cluster-1) had HRQoL scores that were 0.14 points lower than those without CVD/arthritis. After adjusting for sex, age, BMI, labour force status, level of exercise (not in the model of cluster-2), registered marital status, smoking status and socio-economic disadvantage index, multivariate analyses revealed the associations between the HRQoL scores and each cluster remained significant; the MM2+ cluster (coef: -0.18, SE=0.01; p<0.01) and the MM3+ cluster (coef: -0.23, SE=0.02; p<0.01) were higher than the CVD/arthritis cluster (coef: -0.10, SE=0.01; p<0.001) but lower than the MDD/anxiety cluster (coef: -0.36, SE=0.01; p<0.001). (Table 6-7)

## 3.5 Discussion

Consistent with the findings of the 2004 systematic review by Fortin et al. [9], our analysis of a large, nationally representative dataset showed that multimorbidity is common and significantly associated with lower HRQoL. Although the different definitions of multimorbidity did not change this association, the sociodemographic profiles and HRQoL scores varied depending on the definition of multimorbidity. In the present study, the HRQoL scores were lowest in the participants characterized by cluster-2 (MDD/anxiety disorders), followed by MM2+, which defined multimorbidity as 2+ condition entities, and cluster-1 (CVD/arthritis).

Although this study failed to identify a specific cluster of comorbid mental and physical disorders, previous research has demonstrated that the co-occurrence of mental and physical disorders is strongly associated with poorer HRQoL [30]. Therefore, the findings of this study suggest that the count method does not take the type of chronic conditions into account. Therefore, this method can detect the overall influence of multimorbidity on the HRQoL, but it does not capture the specific disease that contributes to the associated HRQoL.

Individual disease-based treatments can help relieve associated discomfort, slow the course of disease and increase the HRQoL for people with a single chronic condition. However, for individuals with multimorbidity, traditional, individual, disease-focused treatment does not perform well due to interactions between the diseases and treatments. Moreover, reducing the number of conditions does not provide health professionals with an effective therapeutic plan. Furthermore, when calculating the burden of multimorbidity, the condition needs to be treated in its entirety if it is to inform accurate health care planning.

Different cut-off values of the number-based count definition of multimorbidity have been used in the previous HRQoL studies [31]. Some of them used both two or more (2+) and three or more (3+) chronic conditions at the same time [16, 32-34] as the cut off value. Harrison, Britt [16] reported that the 2+ definition was more appropriate in a broader age-scope population, whereas 3+ was more specific for an elderly study population [16]. However, no cut-off can be used without caution, particularly because the number of conditions in the current studies ranged from 4 to 102 [34, 35]. Furthermore, the 2+ cut-off is recommended when a limited number of chronic conditions are included in the definition of multimorbidity, whereas the 3+ cut-off requires the inclusion of more chronic conditions [16]. Despite these issues, the 2+ cut-off was deemed most appropriate for our study based on the data used, i.e., eight chronic conditions and a population-based sample.

In addition to hierarchical clustering, other approaches to the common clusters of multimorbidity exist including factor analysis, principal component analysis and K-means clustering [17]. This study used hierarchical clustering with Jaccard's coefficient due to the shared risk factors among the chronic conditions and the binary nature of chronic diseases [20]. However, the other three approaches were tested in a sensitivity analysis using the same sample (results not shown). The same clusters were produced by the factor analysis and principal component analysis: CVD/arthritis (cluster-1) and cancer/stroke/CVD/arthritis/diabetes. K-means analysis produced clusters including cancer/stroke/CVD/arthritis/diabetes and cancer/stroke/CVD/diabetes/MDD/anxiety. Cancer/stroke/CVD/arthritis/diabetes and cancer/stroke/CVD/diabetes/MDD/anxiety were not examined further due to the extremely low prevalence, with only five and two cases, respectively. These differences may be due to the different mechanisms of

the methods used to detect the clusters, i.e., the cluster analysis processes used distance measures, whereas the factor analysis and principal component analysis processes used correlations. In addition, the individuals within these distance-based clusters have more common characteristics. Furthermore, because the results of the hierarchical cluster approach may be sensitive to the distance scales and linking methods, we performed sensitivity analyses using an additional four distance scales: Ward's linkage, waverage linkage, single linkage and complete linkage. All of these scales produced the same results as average linkage, except for single linkage. To test the sensitivity of different cut-off of count-based method, MM3+ as the complex multimorbidity in literature was used as well. [16] The results shown that even prevalence of multimorbidity as well as the mean HRQoL scores in the people considered as multimorbid varied by the different cut-off of multimorbidity used, multivariate analyses revealed similar patterns in the variations of estimates of HRQoL scores within each of the subgroups of individuals considered. In relation to the cluster definitions of multimorbidity, the method does not pre-specify number of conditions but is statistically derived, thus these analyses remain unchanged.

This study has several notable limitations. First, the findings of multimorbidity studies must be in considered with reference to the list of conditions included in the definition of multimorbidity, as the prevalence of multimorbidity depends on the definition used. [35] However, the health conditions used in this study were chosen because they contribute significantly to the burden of disease in the Australian community. Moreover, the present study excluded acute conditions, which some previous studies have included [7]. Although including more conditions in the definition of multimorbidity may potentially provide a more comprehensive understanding of an individual's health status, acute conditions were not considerate in this study as they may only influence health status temporarily [16] and not be relevant to long-term health care planning.

Second, the data used in this study were derived from a survey focused on mental health well-being. As a result, the assessments of physical chronic conditions were relatively brief, self-reported and not verified using medical records [12]. Physical conditions were assessed by self-report in the past 12-months, which may be underestimated or overestimated due to recall bias. However, the validity of self-

reported chronic conditions has been indicated in different contexts. [36-40] Moreover, self-reported data offers cost-effectiveness and convenience for gathering information in the population-based surveys. [41] Finally, despite being encouraged [33], the severity of chronic conditions was not included in this study because it was not measured in the NSMHWB2007 and the additional burden on the respondents (time consuming) may reduce the response rate. Although it is unlikely to change the present status of the condition when defining multimorbidity, the severity may have influenced the HRQoL scores.

To our knowledge, this is the first study to compare number-based and cluster-based definitions of multimorbidity using nationally representative data. This large population-based database, using the delete-1 group jack-knife technique to generate the replicate weights, increases the generalizability of the study's findings and could inform the investigation of multimorbidity-related HRQoL in Australia and similar economies worldwide.

## 3.6 Conclusions

Our findings confirm the existence of an inverse relationship between multimorbidity and HRQoL in the Australian population and indicate that the sociodemographic profile and HRQoL vary depending on the method used to define multimorbidity. We conclude that from this head-to-head comparison, the hierarchical clustering approach has been validated when the outcome of interest is HRQoL. Moreover, a simple count fails to identify if there are specific conditions of interest that are driving lower HRQoL. From this perspective, the cluster-based methods, resulting in clusters with the same shared health conditions, may be more useful and informative. Finally, we recommend that researchers exercise caution when selecting a definition of multimorbidity because it may significantly influence the study outcomes.

**Table 3-1.** Demographic characteristics of the study population, weighted (N=8,820).

| | n | % | Jack-knife standard error |
|---|---|---|---|
| **Sex** | | | |
| Male | 4,018 | 49.7 | 0.01 |
| Female | 4,802 | 50.4 | 0.01 |
| **Age** | | | |
| Mean of age (yr.) | 44 | | 0.04 |
| 16-25yr. | 1,551 | 17.4 | 0.3 |
| 26-35yr | 1,386 | 18.0 | 0.3 |
| 36-45yr. | 1,586 | 19.0 | 0.4 |
| 46-55yr. | 1,247 | 17.5 | 0.3 |
| 56-65yr. | 1,293 | 14.2 | 0.2 |
| 66-75yr. | 1,069 | 8.7 | 0.2 |
| 76-85yr. | 688 | 5.2 | 0.1 |
| **BMI ($kg/m^2$)** | | | |
| Thinness (BMI<18.5) | 254 | 2.7 | 0.2 |
| Normal (BMI 18.5-24.99) | 3,701 | 42.1 | 0.8 |
| Overweight (BMI 25.00-29.99) | 2,965 | 34.7 | 0.7 |
| Obesity (BMI >30.00) | 1,724 | 20.5 | 0.6 |
| **Educational attainment** | | | |
| Has post-school qualification | 4,914 | 54.8 | 0.5 |
| No post-school qualification | 3,906 | 45.2 | 0.5 |
| **Labour force** | | | |
| Employed | 5,491 | 65.2 | 0.2 |
| Unemployed | 215 | 2.6 | 0.1 |
| Not in the labour force | 3,114 | 32.2 | 0.2 |
| **Level of exercise** | | | |
| High | 597 | 7.1 | 0.4 |
| Moderate | 1,754 | 20.2 | 0.7 |
| Low | 6,463 | 72.7 | 0.9 |
| **Registered marital status** | | | |
| Unmarried | 3,996 | 47.0 | 0.7 |
| Married | 4,824 | 53.0 | 0.7 |
| **Smoking status** | | | |
| Current smoker | 1,875 | 22.3 | 0.7 |
| Ex-smoker | 2,513 | 26.9 | 0.7 |
| Never smoked | 4,432 | 50.8 | 0.7 |
| **Index of Socio-Economic Disadvantage - Area deciles** | | | |
| 1st decile (lowest) | 735 | 8.1 | 0.6 |
| 2nd decile | 789 | 8.6 | 0.8 |
| 3rd decile | 975 | 10.4 | 0.8 |
| 4th decile | 777 | 8.1 | 0.8 |
| 5th decile | 897 | 9.7 | 0.8 |
| 6th decile | 890 | 10.3 | 0.9 |
| 7th decile | 862 | 10.0 | 1.0 |
| 8th decile | 989 | 11.8 | 1.0 |
| 9th decile | 896 | 11.0 | 0.8 |
| 10th decile (best) | 1,010 | 12.0 | 0.9 |
| **Number of health conditions** | | | |
| 0 | 3,556 | 43.3 | 0.8 |
| 1 | 2,725 | 30.7 | 0.8 |
| 2 | 1,501 | 15.8 | 0.5 |
| 3 | 697 | 6.8 | 0.3 |
| 4 | 239 | 2.5 | 0.3 |
| 5 | 79 | 0.6 | 0.08 |
| 6 | 20 | 0.2 | 0.06 |
| 7 | 3 | 0.02 | 0.01 |

BMI=Body Mass Index. Sample size (n) are showed based on the raw data, proportion (%) are estimated with standard error based on the weighting strategy.

**Table 3-2.** Prevalence of single chronic conditions and the percentage with other chronic conditions, weighted (N=8,820).

| Chronic conditions | n | % | Jack-knife standard error | % with other listed conditions |
|---|---|---|---|---|
| Asthma | 1,783 | 19.6 | 0.5 | 49.0 |
| Cancer | 882 | 8.3 | 0.4 | 70.6 |
| Stroke | 234 | 2.0 | 0.1 | 91.6 |
| CVD | 2,059 | 21.2 | 0.7 | 69.9 |
| Arthritis | 1,989 | 19.9 | 0.6 | 72.7 |
| Diabetes | 700 | 7.5 | 0.4 | 77.5 |
| MDD | 658 | 7.2 | 0.4 | 82.3 |
| Anxiety Disorder | 1,005 | 11.4 | 0.4 | 71.0 |

Heart or circulatory condition=CVD. Major depression disorder =MDD. Sample size (n) are showed based on the raw data, proportion (%) are estimated with standard error based on the weighting strategy.

**Table 3-3.** Prevalence of common clusters using count method and hierarchical cluster, weighted (N=8,820).

| | Components | n | Prevalence (%) | Jack-knife standard error | Methods |
|---|---|---|---|---|---|
| MM2+ | any 2 (+) of 8 chronic conditions[a] | 2,539 | 26.0 | 0.6 | Count method |
| MM3+ | any 3 (+) of 8 chronic conditions[b] | 1,042 | 10.1 | 0.5 | Count method |
| Cluster 1 | CVD/Arthritis | 934 | 9.1 | 0.5 | Hierarchical cluster |
| Cluster 2 | MDD/Anxiety Disorder | 399 | 4.3 | 0.3 | Hierarchical cluster |

CVD=Heart or circulatory condition. MDD=Major depression disorder. MM=multimorbidity. Sample size (n) are showed based on the raw data, proportion (%) are estimated with standard error based on the weighting strategy.

a: MM2+ which means having any 2 or more chronic conditions out of asthma, cancer, stroke, CVD, gout rheumatism or arthritis and diabetes or high sugar levels, MDD and anxiety disorder.

b: MM3+ which means having any 3 or more chronic conditions out of asthma, cancer, stroke, CVD, gout rheumatism or arthritis and diabetes or high sugar levels, MDD and anxiety disorder.

**Table 3-4.** Mean of AQoL-4D utility scores by sample characteristics using count method to identify multimorbidity, weighted (N=8,820).

| | MM2+[a] | | | MM3+[b] | | |
|---|---|---|---|---|---|---|
| | % | Mean | Jack-knife standard error | % | Mean | Jack-knife standard error |
| **Sex** | | | | | | |
| Male | 23.8 | 0.72 | 0.01 | 8.7 | 0.65 | 0.02 |
| Female | 27.9 | 0.69 | 0.01 | 11.4 | 0.61 | 0.01 |
| **Age** | | | | | | |
| Mean of age (yr.) | | 54.6 | 0.3 | | 57.5 | 0.6 |
| 16-25yr. | 8.9 | 0.68 | 0.03 | 2.4 | 0.56 | 0.09 |
| 26-35yr | 14.1 | 0.67 | 0.02 | 3.3 | 0.54 | 0.05 |
| 36-45yr. | 18.7 | 0.67 | 0.03 | 6.9 | 0.60 | 0.07 |
| 46-55yr. | 26.6 | 0.68 | 0.02 | 9.5 | 0.57 | 0.03 |
| 56-65yr. | 42.2 | 0.73 | 0.01 | 18.7 | 0.66 | 0.02 |
| 66-75yr. | 52.8 | 0.75 | 0.01 | 23.1 | 0.70 | 0.02 |
| 76-85yr. | 58.5 | 0.70 | 0.02 | 27.7 | 0.63 | 0.02 |
| **BMI ($kg/m^2$)** | | | | | | |
| Thinness (BMI<18.5) | 19.2 | 0.63 | 0.06 | 5.3 | 0.34 | 0.10 |
| Normal (BMI 18.5-24.99) | 20.3 | 0.71 | 0.01 | 6.2 | 0.66 | 0.02 |
| Overweight (BMI 25.00-29.99) | 25.7 | 0.71 | 0.01 | 10.8 | 0.64 | 0.03 |
| Obesity (BMI >30.00) | 38.4 | 0.70 | 0.01 | 17.4 | 0.60 | 0.02 |
| **Educational attainment** | | | | | | |
| Has post-school qualification | 23.8 | 0.72 | 0.01 | 8.5 | 0.66 | 0.02 |
| No post-school qualification | 28.4 | 0.69 | 0.01 | 12.1 | 0.60 | 0.02 |
| **Labour force** | | | | | | |
| Employed | 18.2 | 0.74 | 0.01 | 5.6 | 0.64 | 0.02 |
| Unemployed | 20.5 | 0.63 | 0.04 | 8.7 | 0.60 | 0.07 |
| Not in the labour force | 42.0 | 0.68 | 0.01 | 19.4 | 0.62 | 0.02 |
| **Level of exercise** | | | | | | |
| High | 17.2 | 0.75 | 0.02 | 7.1 | 0.67 | 0.04 |
| Moderate | 23.1 | 0.77 | 0.02 | 8.0 | 0.69 | 0.04 |
| Low | 27.5 | 0.69 | 0.01 | 10.9 | 0.61 | 0.01 |
| **Registered marital status** | | | | | | |
| Unmarried | 22.9 | 0.64 | 0.01 | 9.1 | 0.57 | 0.02 |
| Married | 28.4 | 0.75 | 0.01 | 10.9 | 0.67 | 0.02 |
| **Smoking status** | | | | | | |
| Current smoker | 26.5 | 0.62 | 0.02 | 10.7 | 0.53 | 0.03 |
| Ex-smoker | 32.8 | 0.72 | 0.01 | 14.2 | 0.66 | 0.02 |
| Never smoked | 21.8 | 0.74 | 0.01 | 7.6 | 0.66 | 0.02 |
| **Index of Socio-Economic Disadvantage - Area deciles** | | | | | | |
| 1st decile (lowest) | 29.9 | 0.62 | 0.03 | 15.8 | 0.54 | 0.05 |
| 2nd decile | 27.1 | 0.66 | 0.03 | 10.6 | 0.62 | 0.03 |
| 3rd decile | 29.1 | 0.65 | 0.02 | 13.6 | 0.59 | 0.03 |
| 4th decile | 28.9 | 0.66 | 0.03 | 10.8 | 0.59 | 0.03 |
| 5th decile | 29.8 | 0.70 | 0.02 | 13.0 | 0.64 | 0.03 |
| 6th decile | 25.5 | 0.74 | 0.02 | 9.5 | 0.70 | 0.07 |
| 7th decile | 26.1 | 0.72 | 0.03 | 9.4 | 0.64 | 0.04 |
| 8th decile | 24.1 | 0.76 | 0.02 | 6.8 | 0.66 | 0.03 |
| 9th decile | 21.0 | 0.76 | 0.02 | 6.6 | 0.67 | 0.03 |
| 10th decile (best) | 20.6 | 0.77 | 0.02 | 7.2 | 0.67 | 0.04 |

CVD=Heart or circulatory condition. MDD=Major depression disorder. BMI=Body Mass Index. MM=multimorbidity. Means are estimated with standard error based on the weighting strategy.
a: MM2+=2+ conditions.
b: MM3+=3+ conditions.

**Table 3-5.** Mean of AQoL-4D utility scores by sample characteristics using hierarchical cluster to identify multimorbidity, weighted (N=8,820).

| | Cluster-1[a] | | | Cluster-2[b] | | |
|---|---|---|---|---|---|---|
| | % | Mean | Jack-knife standard error | % | Mean | Jack-knife standard error |
| **Sex** | | | | | | |
| Male | 8.6 | 0.75 | 0.02 | 3.7 | 0.54 | 0.04 |
| Female | 9.6 | 0.68 | 0.01 | 4.8 | 0.52 | 0.02 |
| **Age** | | | | | | |
| Mean of age (yr.) | | 63.8 | 0.7 | | 41.7 | 0.7 |
| 16-25yr. | 0.4 | 0.41 | 0.40 | 3.4 | 0.57 | 0.03 |
| 26-35yr | 0.6 | 0.72 | 0.10 | 4.6 | 0.57 | 0.04 |
| 36-45yr. | 3.6 | 0.75 | 0.12 | 6.9 | 0.54 | 0.05 |
| 46-55yr. | 6.6 | 0.68 | 0.03 | 4.7 | 0.49 | 0.05 |
| 56-65yr. | 20.3 | 0.72 | 0.02 | 3.4 | 0.44 | 0.06 |
| 66-75yr. | 28.3 | 0.75 | 0.01 | 2.0 | 0.53 | 0.05 |
| 76-85yr. | 34.7 | 0.66 | 0.02 | 0.6 | 0.24 | 0.13 |
| **BMI ($kg/m^2$)** | | | | | | |
| Thinness (BMI<18.5) | 5.9 | 0.58 | 0.17 | 5.5 | 0.40 | 0.10 |
| Normal (BMI 18.5-24.99) | 4.8 | 0.73 | 0.02 | 4.5 | 0.60 | 0.03 |
| Overweight (BMI 25.00-29.99) | 9.5 | 0.73 | 0.02 | 3.4 | 0.47 | 0.04 |
| Obesity (BMI >30.00) | 17.8 | 0.68 | 0.02 | 4.8 | 0.48 | 0.03 |
| **Educational attainment** | | | | | | |
| Has post-school qualification | 7.7 | 0.75 | 0.01 | 4.2 | 0.54 | 0.03 |
| No post-school qualification | 10.8 | 0.67 | 0.02 | 4.3 | 0.51 | 0.03 |
| **Labour force** | | | | | | |
| Employed | 4.0 | 0.76 | 0.02 | 3.9 | 0.60 | 0.02 |
| Unemployed | 2.0 | 0.67 | 0.18 | 8.2 | 0.53 | 0.07 |
| Not in the labour force | 20.2 | 0.69 | 0.02 | 4.7 | 0.40 | 0.03 |
| **Level of exercise** | | | | | | |
| High | 4.1 | 0.74 | 0.04 | 3.5 | 0.61 | 0.04 |
| Moderate | 7.8 | 0.82 | 0.03 | 4.4 | 0.50 | 0.05 |
| Low | 10.0 | 0.69 | 0.01 | 4.3 | 0.53 | 0.02 |
| **Registered marital status** | | | | | | |
| Unmarried | 6.5 | 0.64 | 0.02 | 5.9 | 0.49 | 0.02 |
| Married | 11.4 | 0.75 | 0.02 | 2.8 | 0.59 | 0.05 |
| **Smoking status** | | | | | | |
| Current smoker | 5.4 | 0.61 | 0.05 | 8.4 | 0.49 | 0.03 |
| Ex-smoker | 14.7 | 0.72 | 0.02 | 3.6 | 0.54 | 0.05 |
| Never smoked | 7.8 | 0.74 | 0.02 | 2.8 | 0.56 | 0.03 |
| **Index of Socio-Economic Disadvantage - Area deciles** | | | | | | |
| 1st decile (lowest) | 11.5 | 0.59 | 0.06 | 5.9 | 0.44 | 0.06 |
| 2nd decile | 9.7 | 0.69 | 0.03 | 3.1 | 0.46 | 0.05 |
| 3rd decile | 11.0 | 0.66 | 0.03 | 5.6 | 0.42 | 0.06 |
| 4th decile | 9.1 | 0.65 | 0.04 | 6.4 | 0.53 | 0.09 |
| 5th decile | 11.8 | 0.69 | 0.03 | 5.6 | 0.47 | 0.06 |
| 6th decile | 9.2 | 0.81 | 0.05 | 3.5 | 0.59 | 0.04 |
| 7th decile | 10.7 | 0.76 | 0.03 | 4.1 | 0.56 | 0.05 |
| 8th decile | 7.2 | 0.78 | 0.03 | 3.8 | 0.65 | 0.08 |
| 9th decile | 5.3 | 0.77 | 0.04 | 3.0 | 0.59 | 0.07 |
| 10th decile (best) | 7.2 | 0.74 | 0.05 | 2.7 | 0.63 | 0.05 |

CVD=Heart or circulatory condition. MDD=Major depression disorder. BMI=Body Mass Index. MM=multimorbidity. Means are estimated with standard error based on the weighting strategy.
a: Cluster-1= CVD + Arthritis.
b: Cluster-2= MDD + Anxiety Disorder.

**Table 3-6.** Mean of AQoL-4D utility scores and linear associations by sample characteristics using count method to identify multimorbidity, weighted.

| | Univariate analysis | | Model 1 – Present. MM2+[a] Multivariate analysis | | Model 2 – Present. MM3+[b] Multivariate analysis | |
|---|---|---|---|---|---|---|
| | **Unadjusted β[c]** | **Jack-knife standard error** | **Adjusted β[d]** | **Jack-knife standard error** | **Adjusted β[d]** | **Jack-knife standard error** |
| **Sex** | | | | | | |
| Male | Ref. | | Ref. | | Ref. | |
| Female | -0.02 | 0.01 | 0.001 | 0.01 | 0.002 | 0.01 |
| **Age** | | | | | | |
| 16-25yr. | Ref. | | Ref. | | Ref. | |
| 26-35yr. | **-0.04** | **0.01** | **-0.05** | **0.01** | **-0.06** | **0.01** |
| 36-45yr. | **-0.05** | **0.01** | **-0.07** | **0.01** | **-0.08** | **0.01** |
| 46-55yr. | **-0.08** | **0.02** | **-0.09** | **0.01** | **-0.10** | **0.01** |
| 56-65yr. | **-0.09** | **0.01** | **-0.04** | **0.02** | **-0.06** | **0.02** |
| 66-75yr. | **-0.09** | **0.01** | 0.02 | 0.02 | -0.01 | 0.02 |
| 76-85yr. | **-0.19** | **0.02** | -0.05 | 0.03 | **-0.08** | **0.03** |
| p for trend | **<0.05** | | =0.20 | | **<0.05** | |
| **BMI (kg/m$^2$)** | | | | | | |
| Thinness (BMI<18.5) | -0.08 | 0.05 | -0.01 | 0.01 | -0.05 | 0.03 |
| Normal (BMI 18.5-24.99) | Ref. | | Ref. | | | |
| Overweight (BMI 25.00-29.99) | 0.03 | 0.01 | -0.02 | 0.01 | -0.01 | 0.01 |
| Obesity (BMI >30.00) | **-0.01** | **0.02** | **-0.02** | **0.01** | **-0.02** | **0.01** |
| p for trend | **<0.05** | | =0.30 | | =0.30 | |
| **Labour force status** | | | | | | |
| Employed | Ref. | | Ref. | | Ref. | |
| Unemployed | -0.05 | 0.03 | -0.02 | 0.03 | -0.02 | 0.03 |
| Not in the labour force | **-0.13** | **0.01** | **-0.11** | **0.02** | **-0.10** | **0.02** |
| **Level of exercise** | | | | | | |
| High | Ref. | | Ref. | | Ref. | |
| Moderate | -0.003 | 0.02 | 0.01 | 0.02 | 0.004 | 0.02 |
| Low | **-0.06** | **0.02** | -0.03 | 0.02 | -0.03 | 0.02 |
| **Registered marital status** | | | | | | |
| Unmarried | Ref. | | Ref. | | Ref. | |
| Married | **0.05** | **0.01** | **0.08** | **0.01** | **0.08** | **0.01** |
| **Smoking status** | | | | | | |
| Current smoker | Ref. | | Ref. | | Ref. | |
| Ex-smoker | **0.04** | **0.01** | **0.04** | **0.02** | **0.04** | **0.01** |
| Never smoked | **0.09** | **0.01** | **0.06** | **0.01** | **0.06** | **0.01** |
| **Index of Socio-Economic Disadvantage - Area deciles** | | | | | | |
| 1st decile (lowest) | Ref. | | Ref. | | Ref. | |
| 2nd decile | 0.01 | 0.02 | -0.002 | 0.02 | -0.01 | 0.02 |
| 3rd decile | -0.01 | 0.02 | -0.03 | 0.02 | -0.03 | 0.02 |
| 4th decile | 0.01 | 0.03 | -0.01 | 0.02 | -0.01 | 0.02 |
| 5th decile | 0.03 | 0.02 | 0.002 | 0.02 | -0.003 | 0.02 |
| 6th decile | 0.03 | 0.02 | -0.01 | 0.02 | -0.02 | 0.02 |
| 7th decile | **0.05** | **0.02** | 0.02 | 0.02 | 0.01 | 0.02 |
| 8th decile | **0.07** | **0.02** | 0.02 | 0.02 | 0.01 | 0.02 |
| 9th decile | **0.07** | **0.03** | 0.01 | 0.02 | 0.01 | 0.02 |
| 10th decile (best) | **0.09** | **0.02** | 0.02 | 0.02 | 0.01 | 0.02 |
| p for trend | **<0.05** | | **<0.05** | | **<0.05** | |
| | | | | | | |
| **Present. MM2+[a]** | **-0.21** | **0.01** | **-0.18** | **0.01** | | |
| **Present. MM3+[a]** | **-0.26** | **0.02** | | | **-0.23** | **0.02** |
| **Observations** | | | 8,605 | | 8,605 | |
| **Weighted R$^2$** | | | **0.1219** | | **0.1159** | |

BMI=Body Mass Index.

Means are estimated with standard error based on weighting strategy.

a: MM2+=2+ conditions.

b: MM3+=3+ conditions.

c: β from univariate linear regression for the associations with HRQoL.

d: β from multivariate linear regression model with all other variables in the table adjusted for the associations with HRQoL.

Significant coefficients are typed in bold font (p<0.05).

**Table 3-7.** Mean of AQoL-4D utility scores and linear associations by sample characteristics using hierarchical cluster to identify multimorbidity, weighted.

| | Univariate analysis | | Model 3 – Cluster-1[a] Multivariate analysis | | Model 4 – Cluster-2[a] Multivariate analysis | |
|---|---|---|---|---|---|---|
| | **Unadjusted β[b]** | **Jack-knife standard error** | **Adjusted β[c]** | **Jack-knife standard error** | **Adjusted β[c]** | **Jack-knife standard error** |
| **Sex** | | | | | | |
| Male | Ref. | | Ref. | | Ref. | |
| Female | -0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| **Age** | | | | | | |
| 16-25yr. | Ref. | | Ref. | | Ref. | |
| 26-35yr. | **-0.04** | **0.01** | **-0.06** | **0.01** | **-0.05** | **0.01** |
| 36-45yr. | **-0.05** | **0.01** | **-0.09** | **0.01** | **-0.08** | **0.01** |
| 46-55yr. | **-0.08** | **0.02** | **-0.13** | **0.01** | **-0.12** | **0.01** |
| 56-65yr. | **-0.09** | **0.01** | **-0.08** | **0.01** | **-0.09** | **0.01** |
| 66-75yr. | **-0.09** | **0.01** | -0.03 | 0.02 | **-0.06** | **0.02** |
| 76-85yr. | **-0.19** | **0.02** | **-0.08** | **0.02** | **-0.12** | **0.02** |
| p for trend | **<0.05** | | **<0.05** | | **<0.05** | |
| **BMI (kg/m$^2$)** | | | | | | |
| Thinness (BMI<18.5) | -0.08 | 0.05 | -0.05 | 0.02 | -0.05 | 0.02 |
| Normal (BMI 18.5-24.99) | Ref. | | Ref. | | Ref. | |
| Overweight (BMI 25.00-29.99) | 0.03 | 0.01 | -0.01 | 0.01 | -0.02 | 0.01 |
| Obesity (BMI >30.00) | **-0.01** | **0.02** | **-0.05** | **0.01** | **-0.05** | **0.01** |
| p for trend | **<0.05** | | **<0.05** | | **<0.05** | |
| **Labour force status** | | | | | | |
| Employed | Ref. | | Ref. | | Ref. | |
| Unemployed | -0.05 | 0.03 | -0.06 | 0.02 | -0.04 | 0.02 |
| Not in the labour force | **-0.13** | **0.01** | **-0.12** | **0.01** | **-0.11** | **0.01** |
| **Level of exercise[d]** | | | | | | |
| High | Ref. | | Ref. | | | |
| Moderate | -0.003 | 0.02 | 0.01 | 0.02 | | |
| Low | **-0.06** | **0.02** | -0.03 | 0.02 | | |
| **Registered marital status** | | | | | | |
| Unmarried | Ref. | | Ref. | | Ref. | |
| Married | **0.05** | **0.01** | **0.09** | **0.01** | **0.07** | **0.01** |
| **Smoking status** | | | | | | |
| Current smoker | Ref. | | Ref. | | Ref. | |
| Ex-smoker | **0.04** | **0.01** | **0.05** | **0.01** | **0.04** | **0.01** |
| Never smoked | **0.09** | **0.01** | **0.07** | **0.01** | **0.06** | **0.01** |
| **Index of Socio-Economic Disadvantage - Area deciles** | | | | | | |
| 1st decile (lowest) | Ref. | | Ref. | | Ref. | |
| 2nd decile | 0.01 | 0.02 | 0.002 | 0.02 | 0.01 | 0.02 |
| 3rd decile | -0.01 | 0.02 | 0.001 | 0.02 | 0.01 | 0.02 |
| 4th decile | 0.01 | 0.03 | 0.01 | 0.02 | 0.02 | 0.02 |
| 5th decile | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| 6th decile | 0.03 | 0.02 | 0.01 | 0.02 | 0.02 | 0.02 |
| 7th decile | **0.05** | **0.02** | 0.02 | 0.02 | 0.03 | 0.02 |
| 8th decile | **0.07** | **0.02** | 0.04 | 0.02 | 0.04 | 0.02 |
| 9th decile | **0.07** | **0.03** | 0.03 | 0.02 | 0.04 | 0.02 |
| 10th decile (best) | **0.09** | **0.02** | 0.04 | 0.02 | 0.05 | 0.02 |
| p for trend | **<0.05** | | **<0.05** | | **<0.05** | |
| | | | | | | |
| **Present. Cluster1[a]** | **-0.14** | **0.02** | **-0.10** | **0.01** | | |
| **Present. Cluster2[a]** | **-0.38** | **0.02** | | | **-0.36** | **0.01** |
| **Observations** | | | 8605 | | 8605 | |
| **Weighted R$^2$** | | | **0.0773** | | **0.1427** | |

CVD=Heart or circulatory condition. MDD=Major depression disorder. BMI=Body Mass Index. MM=multimorbidity.

a: Cluster-1= CVD + Arthritis; Cluster-2= MDD + Anxiety Disorder.

b: β from univariate linear regression for the associations with HRQoL.

c: β from multivariate linear regression models with all other variables in the table adjusted for the associations with HRQoL.

d: "level of exercise" was not included in model-4 because it was excluded in confounder selection.

Significant coefficients are typed in bold font (p<0.05).

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# Chapter 4. How Australian employees use health services of single disease when suffering from multimorbidity: Findings from the National Health Survey

## 4.1 Preface

This chapter aims to understand the patterns of healthcare service utilization in employees with multimorbidity, we: i) characterized diseases according to their comorbidity statuses (one-condition or coexisting chronic conditions); and ii) determined the associations between multimorbidity and disease-specific healthcare service utilization. This work is important, as it is the first to examine the associations between multimorbidity and disease-specific healthcare utilization in a nationally representative sample of the working population. As the number of employed individuals managing work and chronic illness is increasing, these findings can help shape future occupational and health services.

The text that follows is included in a manuscript that has been published in a peer-reviewed journal [1].

## 4.2 Introduction

Multimorbidity, or the presence of multiple chronic conditions in one individual, is a major public health concern [2-4] due to its increasing prevalence, associated cost, and often complex medical management.[5] Multimorbidity is more common in older age groups [3, 6]. However, more than half of individuals with multimorbidity are younger than 65 years of age (i.e., of working age) [7]. The earlier onset of chronic conditions also implies younger persons are more likely to experience subsequent chronic conditions [4, 8]. Most direct healthcare costs in health systems are spent on treating multimorbidity [5, 9]. In addition employees, who represent 63.4% of the global population, are working longer than before, even though have reached their retirement age [10]. For example, the Australian labour force participation rate for individuals aged

55+ years rose from 23% in 1984 to 35% in 2014 [11], and one fifth of Australian adults had multimorbidity[11]. Moreover, for males in the 65-74-year-old group, this rate increased 11% from 2002-03 to 2011-12; for females, while an increase across all age groups has been observed, the largest increase happened in the older age groups [12]. Therefore, multimorbidity has become a substantial and challenging health and economic issue for the current workforce.

People with multimorbidity have higher overall health service utilization, including more frequent and longer hospitalizations, readmissions, and physician visits, than people with a single condition [2, 3, 6, 13-15]. However, healthcare service utilization is multifactorial and potentially subject to measurement error [16]. The more health conditions a person experiences, the higher the risk of measurement error. As healthcare is still predominately delivered according to the individual diseases [3], it is useful to understand healthcare service utilisation patterns for diseases when they are multimorbid versus not. Additionally, most studies have focused on higher risk populations, such as patients who frequently use healthcare services and the elderly, who are more likely to present with multimorbidity [17]. As a productive workforce is central to the economic well-being of a country, understanding how employees use healthcare services for single diseases in the context of multimorbidity is essential. Particularly to gain the insights into their healthcare demands and reduce the consequences of multimorbidity on the workforce, including absenteeism, presenteeism and the related lost productive time. However, we were unable to locate any studies that reported the associations between multimorbidity and disease-specific healthcare service utilization, which referred to a series of single-disease evaluations, particularly in the workforce.

Until recently, the definition of multimorbidity and the included number of health conditions studies varied across the studies as no agreed definition existed[4]. Some international institutes, such as the Academy of Medical Sciences[18] are calling for evidence to progress a consistent definition of multimorbidity. The consequence of no unique definition makes the comparison between studies challenging. Therefore, it is critical to specify the definition of multimorbidity and the included number of health conditions in the studies focusing on multimorbidity.

The aim of this study was to examine the association of multimorbidity with disease-specific healthcare service utilization in a working population. Specifically, we sought to: i) characterize employees with a specific chronic condition in terms of their health statuses (with or without multimorbidity); and ii) determine the associations between the presence of multimorbidity and disease-specific healthcare service utilization among employees.

## 4.3 Methods

### 4.3.1 Study design and participants

Data were derived from the nationally representative, cross-sectional Australian National Health Survey (NHS), which was conducted from March 2011 to March 2012 [19]. Initially, 21,108 private dwellings were selected in the sample. This number was reduced to 18,355 due to sample loss in the field stage [19]. Of these dwellings, 15,565 (84.8%) were fully or adequately responding households, including 20,426 persons aged 0 years and over [19]. Under or over-representation of particular demographic groups, such as working people (under-represented as the survey was conducted in private dwellings), was adjusted to ensure sample representativeness[19].

The NHS dataset contains self-reported information on the labour force status and healthcare service utilization for each current chronic disease in the 12 months prior to the face-to-face interviews conducted among respondents aged 15 years and over [19]. Respondents were classified as employed, unemployed, or not in the labour force using the reduced set of the questions from the ABS Monthly Labour Force Survey [19]. Employed respondents were identified when they had worked in a job, for a business, or on a farm in the past week, or had a job but were absent during that week [19]. However, respondents whose usual work time was less than one hour, unpaid voluntary work, and those who were away from work due to workers' compensation but were unsure whether they would return to work for their employers were excluded [19]. Therefore, for the purpose of this study, respondents aged 15 years and older who were currently employed at the time of interview were included.

### 4.3.2 Multimorbidity

Multimorbidity was defined as the concurrent presence of two or more diagnosed chronic conditions [20-22]. Eight diagnosed chronic conditions that had lasted, or were expected to last, six months or more based on a computer-based coding system developed by the ABS were collected, including asthma, cancer, CVD, arthritis, osteoporosis, diabetes (type 2, type 1 and unspecified type-excluding diabetes which was not current, long-term and diagnosed, such as gestational diabetes and diabetes insipidus), kidney disease, and mental disorders; these conditions were the most commonly experienced and were relevant to policy planning in the Australian community. The aforementioned conditions were identified as chronic medical conditions by asking whether the patient had "ever been told by a doctor or nurse, still current and long-term" and then by asking whether "had lasted at least six months or the respondent expected the condition to last six months or longer". There were exceptions for some conditions (e.g., asthma was considered even if the respondent reported that asthma was not a current condition but had either experienced symptoms/treatment in the past 12 months or answered 'yes' to whether they still had asthma attacks).

### 4.3.3 Healthcare service utilization

Information on healthcare service utilization for consultations, including the frequency of visits in the past 12 months, was collected for each respondent and each chronic condition mentioned above. Self-reported information was collected concerning visits to some health professionals [GPs (general practitioners) and specialists (e.g., a cardiologist for CVD)], whereas other health professionals (e.g., nurses and social workers) were grouped into one category with binary answers reporting whether they had been visited at least once in the past 12 months. Information for each HSU was recorded only once for each condition group per respondent. However, because the respondent might visit a health professional for several different conditions during one visit, the number of visits for different conditions could not be summed to estimate total number of visits for a given individual. For example, a respondent who reported having visited a GP five times for

CVD and two times for diabetes might have a total number of GP visits ranging from five to seven.

### 4.3.4 Covariates

Univariate analyses with a 0.25 p-value cut-off were performed to identify covariates before the second round of screening, which involved multivariate analyses. A cut-off of a 10% change in the exposure variable's coefficient estimate in the multivariate model was adopted to identify "important" variables that influenced the association between the outcome and the exposure. Covariates that remained after these procedures were utilized in all subsequent analyses conducted in this study. The following covariates were included in this study: age, gender, non-school qualification (having a non-school qualification, including a postgraduate degree, graduate diploma/graduate certificate, bachelor degree, advanced diploma/diploma, certificate III/IV, or certificate I/II, having a certificate that was not further defined, and not having a non-school qualification), and body mass index (BMI=self-reported weight/self-reported height$^2$).

### 4.3.5 Statistical analyses

Means, frequencies, and percentages were used in the descriptive analyses. To explore the associations of multimorbidity and disease-specific healthcare service utilization, logistic and Poisson regression models were used to compare individuals who had only one specific chronic condition to multimorbid individuals who had that specific chronic condition. Odds ratios were estimated from the logistic regression models for visits with other health professionals (excluding GPs and specialists), and relative rates were estimated from the Poisson regression models for GP and specialist visits.

To account for non-responses, national representativeness, and confidentiality, all analyses were weighted using replicate weights to infer the results for the total in-scope Australian population [19]. All standard errors (SEs) of the estimates were generated by the delete-A-group jack-knife technique [19]. The significance level was set at $\alpha$=0.05. Multiple testing was not adjusted[23], as this study is an exploratory

study, which is mainly for hypothesis generating. The analyses were performed in STATA version 10, special edition (StataCorp, College Station, TX, USA) [24].

## 4.4 Results

We analysed data from 10,363 employed participants from a nationally representative database. Almost one-quarter of the workforce (23.4%, 95% CI 22.3-24.7) had multimorbidity. Of the workforce reporting multimorbidity, 15.2% (95% CI 14.3-16.1) had two chronic conditions and 8.2% (95% CI 7.5-8.9) had three or more chronic conditions. The most prevalent chronic conditions were CVD at 29.1% (95% CI 27.9-30.4), followed by asthma (20.0%, 95% CI 18.9-21.2) and mental disorders (12.5%, 95% CI 11.7-13.2) (Table 4-1).

Compared to employees with single conditions, the employees with multimorbidity were more likely to be females for the majority of conditions, relatively older, more likely to be educated, less likely to be current smokers, more likely to have a higher BMI, and less likely to be white-collar workers. Moreover, the prevalence of multimorbidity increased with age but was highest in the 45 to 64-year-old age group. The prevalence also increased with the income level, except for cases including mental disorders, which were highest amongst those in the middle-income quintile. There were too few cases of osteoporosis and kidney disease (21 and 22, respectively) to estimate accurately (the 95% CI ranges were quite large) and apply a regression model (Table 4-2).

The percentage of employees, who reported visiting a GP at least once in the previous 12 months prior to the survey interview was higher in most disease groups when multimorbidity was present, compared to when only a single condition was present. In particular, the employees with multimorbidity were more likely to have a higher number of visits. For instance, the employees who visited GPs four times or more times were more likely to suffer from multimorbidity for all listed conditions. The percentage of multimorbid employees who reported visiting any other health professional at least once in the prior 12 months was higher for the employees with cancer, arthritis, osteoporosis, CVD, and kidney disease than for the employees with only one condition in each condition group (Table 4-3).

After controlling for age and gender, multimorbid employees with arthritis had 1.7-fold (95% CI=1.1-2.2, $p<0.001$) greater odds of arthritis-specific healthcare service utilization of GP visits than employees with arthritis alone. Compared with employees with CVD alone, multimorbid employees with CVD had 1.6-fold (95% CI=1.1-2.5, P<0.05) greater odds of CVD-specific specialist visits and 2.5-fold (95% CI=1.5-4.0, P<0.001) greater odds of CVD-specific visits with other healthcare professionals (Table 4-4). Overall, our results suggested that the pattern of disease-specific healthcare service utilization varied by condition.

## 4.5 Discussion

The descriptive analyses from this nationally representative survey revealed that the majority of multimorbid employees reported higher utilization of disease-specific healthcare than the employees with one condition alone, which was consistent with previous studies in different populations [3]. While a strong association between multimorbidity and total healthcare service utilization is well recognized, this study found that multimorbidity does not always increase the healthcare service utilization for a given disease. The association of multimorbidity with healthcare service utilization in employees therefore varies depending on disease type. Examination of these nationally representative data is an important part of understanding the further healthcare needs of the multimorbid working population, but whether these varying healthcare service patterns represent under- or over-utilization of particular services cannot be answered from this cross-sectional survey.

In this study, multimorbid employees with arthritis had more arthritis-specific GP visits than employees with arthritis alone, whereas multimorbid employees with CVD were not more likely to visit GPs but were more likely to visit CVD specialists than employees with CVD alone. Multiple factors can explain these findings. For example, because arthritis in itself is inflammatory and its main symptoms are joint pain and stiffness, these symptoms may impair a person's ability to perform routine tasks [25, 26]. Therefore, adults with multimorbid arthritis are more likely to have adverse outcomes, such as mental distress, and work disability than adults without arthritis [25]. Subsequently, these employees may experience greater and more frequent pain, which

motivates them to use primary healthcare services more often than employees with arthritis alone.

Multimorbid employees with CVD were more likely to visit healthcare professionals (excluding GPs) than employees with CVD alone. One explanation could be that CVD, which is the global leading cause of death [27], typically manifests in acute events, such as heart attacks and strokes [28]. Therefore, adults with CVD who routinely visit their GPs, especially those who are asymptomatic, do not change their service-use models unless they experience an emergency. When acute events do occur, these individuals may require tertiary healthcare, and the odds of an acute event occurring are compounded when CVD is multimorbid. Alternatively, because GPs are considered the "gatekeepers" in the Australian healthcare system, people with multimorbid CVD are referred to specialists according to the GP's professional knowledge and opinion even if they are initially asymptomatic and do not actively require more healthcare services.

Coexisting mental-physical disorders lead to higher healthcare service utilization [29]. However, in this study, multimorbid employees with mental and other chronic disorders did not report a higher utilization of any healthcare service. This finding could be explained by an increase in the utilization of healthcare for physical disorders. In other words, mental disorders themselves are already associated with increased healthcare service utilization [30], and their coexistence with other physical disorders(s) may not further influence the mental disorder-specific healthcare needs. This finding could also be explained by underservicing and the stigma seeking out mental health care. However, the presence of mental disorders could aggravate a person's coexisting physical disorders and thus lead to a corresponding increase in healthcare service utilization. Because most coexisting physical-mental disorders occur in the working-age population [7, 31], the presence of a mental disorder could increase total healthcare service utilization rates by exacerbating a person's symptoms or perceptions of a poor health status even though mental disorder-specific healthcare service utilization did not increase due to multimorbidity. Further, pooling all mental disorder types into one category may have mediated healthcare service utilization for severe mental disorders, such as major depression. Healthcare service utilization for

the other conditions did not differ between employees with multimorbidity and with single conditions alone.

In Australia, employees with multimorbid conditions that include arthritis or CVD require more attention because their additional needs may lead to new diagnoses, prescriptions, and lifestyle changes. Moreover, in the Australian, and other similar healthcare systems, GPs are the gatekeepers of healthcare delivery and play an important role in managing multimorbidity. Therefore, specialists may be unwilling to share their expertise with those outside of their area. Subsequently, to plan for the healthcare of the growing number of employees who juggle both employment and chronic conditions, the provision of integrated and appropriate services by GPs who closely coordinate their patient's care should remain an area of emphasis for future studies.

In contrast to the certainty of single diseases, multimorbidity is more changeable and there is no "one-size-fits-all" method to address all issues arising from it. Unfortunately, health professionals receive no explicit medical education or training in how to prioritize care for persons experiencing multimorbidity. Further, the more chronic conditions employees have, the more diseases they want to address at each consultation, which makes the health professional's ability to make treatment decisions more difficult. However, the length of a standard consultation (5-25 minutes) may not be sufficient for even one disease, and this discrepancy may lead to the under-treatment of some conditions, particularly when they co-exist with others [32, 33].

For employees with multimorbidity, setting disease priorities is unavoidable. The most important step is to determine whether to identify these diseases explicitly and rationally. The needs of an individual with multimorbidity may vary substantially over their life course. Therefore, individuals with CVD or arthritis of working age need more attention and may gain greater health improvements if being managed appropriately. Moreover, the Australian National Health Survey used in this study measured healthcare use for each health conditions, which prohibit the use of "normal" count-based or cluster-based methods of defining multimorbidity [34]. As such, current national population data collection may not address the identified gap.

As Tinetti et al (2012) suggest "healthcare should but not shift its current focus from a disease orientation to a patient goal orientation" [35] and must be updated to align with the clinical reality of multimorbidity.

This study also revealed the prevalence of multimorbidity in the workforce was consistent with previous studies [36] and, whilst it increased with age, was highest in the 45 to 64-year-old age group. This result may have occurred because the employees in this age group are more likely to consent to early retirement when experiencing from multimorbidity. However, the pension they receive may not be sufficient to support their heavy health and economic burdens due to multimorbidity. This could lead to multimorbid employees remaining in the workforce in order to cover the costs associated with their diseases in the very near future [37].

Given no agreed definition, using the other methods to define multimorbidity may have produced different results. For example, using the higher cut-off may strengthen the negative association of multimorbidity with HSU, and it is possible that more health conditions would be identified in addition to arthritis and CVD in this study. However, the three cut-off requires more included health conditions and is more appropriate to older populations whereas the two cut-off is more appropriate in populations with a broader age scope[38]. Another popular method is questionnaire-based, such as the CIRS[39] and Charlson Index[40] which require additional mapping of diagnoses from the classification system[38]. So it is impossible to access these scales if the survey like the NHS 2011-12 does not incorporate them.

A notable limitation of this study was the use of cross-sectional data which meant neither directionality nor temporality could be attributed to the associations between variables, and causal relationships could not be determined. Further, this study was based on self-reported data. That is, diagnoses and healthcare service utilization were not clinically verified by professionals, and the participants were asked only about main conditions to reduce recall bias [19]. However, some conditions were likely under-reported due to stigma (e.g., mental disorders) and the presence of "silent" conditions (e.g., mental/behavioural disorders or diabetes) [41]. Finally, due to the confidential purpose and the complex multistage cluster sampling of the NHS 2011-12 data, some statistical processing such as the differences test between two groups was not allowed

within the ABS on-line data query environment, which may lead to interpretation difficulty to some extent. However, we provided the 95% CI of each estimate to present the magnitude of difference.

The strengths of this study included the use of nationally representative data, which covered approximately 97% of the people living in Australia at the time of the NHS [19]. This broad coverage increases the generalizability of the findings. In contrast to other studies [41, 42], this study explored multimorbidity not only in the working-age population but also in a population who were actually employed at the time of survey completion. This distinction could exclude working-age people who were not in the workforce, who likely had different healthcare service utilization needs, and who were not influenced by work-related factors.

## 4.6 Conclusions

This study is the first to examine the associations between multimorbidity and disease-specific healthcare service utilization using a nationally representative sample of employees and a series of chronic conditions. Multimorbidity was common in this population. Compared with individuals with other diseases, employees with multimorbid conditions including arthritis or CVD required more attention in understanding the associations between multimorbidity and health service use. Guidelines for the management of multimorbidity are urgently needed, especially with the inevitable economic burden imposed by the ageing workforce. Longitudinal studies are recommended to understand the progression and impact of multimorbidity on healthcare resource utilization over time. However, the very first and most important step is updating the way of data collection to align with the clinical reality of multimorbidity.

**Table 4-1.** Percentage of chronic conditions in the Australian working population (2011-12).

| Chronic Conditions | n | % (95% CI) |
|---|---|---|
| CVD | 3,175 | 29.1 (27.9-30.4) |
| Asthma | 2,150 | 20.0 (18.9-21.2) |
| Mental disorder | 1,386 | 12.5 (11.7-13.2) |
| Arthritis | 1,295 | 11.4 (10.7-12.2) |
| Cancer | 1,070 | 9.1 (8.4-9.8) |
| Diabetes | 808 | 7.1 (6.5-7.7) |
| Osteoporosis | 204 | 1.5 (1.2-1.8) |
| Kidney disease | 148 | 1.3 (1.0-1.6) |
| **Number of chronic conditions** | | |
| 0 | 4,163 | 42.4 (41.2-43.7) |
| 1 | 3,506 | 34.1 (32.9-35.3) |
| 2 | 1,726 | 15.2 (14.3-16.1) |
| 3+ | 968 | 8.2 (7.5-8.9) |

CVD=cardiovascular disease. Sample size (n) are showed with crude data, percentage of chronic conditions are estimated with weighting strategy. The sample size of working participants was 10,363.

**Table 4-2.** Distribution of socio-demographic characteristics by morbidity category in a national working population.

| | Asthma | | Cancer | | CVD | | Arthritis | |
|---|---|---|---|---|---|---|---|---|
| | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** |
| | **n=975** | **n=1175** | **n=304** | **n=766** | **n=1,258** | **n=1917** | **n=325** | **n=970** |
| Male (vs. female) | 58.2 (54.0-62.5) | 44.1 (41.2-47.1) | 54.8 (47.9-61.8) | 50.4 (45.8-54.9) | 54.3 (51.1-57.5) | 49.0 (46.3-51.8) | 56.2 (49.4-63.1) | 44.3 (40.2-48.4) |
| **Age** | | | | | | | | |
| 15-24 yrs. | 28.6 (25.0-32.2) | 11.2 (8.4-14.1) | 2.6 (0-5.4) | 1.3 (0.1-2.5) | 5.9 (3.7-8.0) | 4.4 (2.8-6.1) | 4.0 (0.4-7.7) | 1.0 (0.3-1.6) |
| 25-34 yrs. | 33.6 (29.9-37.4) | 20.8 (18.1-23.6) | 6.8 (3.3-10.4) | 7.1 (5.0-9.3) | 18.7 (15.6-21.7) | 9.8 (8.4-11.3) | 8.9 (4.9-13.0) | 7.0 (5.1-8.9) |
| 35-44 yrs. | 19.5 (16.2-22.8) | 22.3 (19.3-25.4) | 28.9 (22.2-35.6) | 13.0 (9.8-16.2) | 23.9 (21.0-26.8) | 18.0 (16.2-19.9) | 16.6 (10.5-22.8) | 11.0 (8.4-13.6) |
| 45-54 yrs. | 12.7 (10.0-15.4) | 22.1 (19.8-24.5) | 32.9 (27.0-38.8) | 24.4 (20.7-28.1) | 28.3 (26.2-30.5) | 28.4 (26.2-30.5) | 33.8 (26.2-41.3) | 29.4 (25.9-32.9) |
| 55-64 yrs. | 5.2 (3.7-6.8) | 18.9 (16.1-21.6) | 23.1 (16.9-29.3) | 40.2 (35.9-44.5) | 18.9 (16.6-21.2) | 30.5 (28.3-32.8) | 27.6 (21.3-33.9) | 39.4 (35.8-42.9) |
| 65+ yrs. | 0.3 (0-0.6) | 4.6 (3.2-6.0) | 5.7 (2.7-8.6) | 13.9 (10.2-17.6) | 4.3 (3.2-5.4) | 8.8 (7.2-10.3) | 9.0 (4.5-13.6) | 12.3 (9.7-14.9) |
| Married (vs. unmarried) | 39.6 (35.9-43.3) | 49.2 (45.1-53.3) | 67.7 (61.9-73.5) | 65.5 (61.0-70.0) | 64.8 (60.9-68.7) | 61.8 (58.6-65.0) | 67.0 (60.1-74.0) | 64.0 (59.7-68.3) |
| Has educational attainment (vs. do not has) | 65.9 (62.2-69.6) | 72,2 (68.9-75.8) | 70.3 (64.4-76.2) | 73.1 (69.2-77.1) | 71.3 (68.3-74.3) | 69.3 (66.6-72.0) | 57.8 (49.1-66.4) | 69.1 (65.5-72.6) |
| Current smoker (vs. non-smoker) | 19.3 (15.8-22.7) | 20.9 (17.9-23.9) | 17.2 (12.5-22.0) | 15.6 (11.9-19.3) | 16.7 (14.0-19.4) | 16.1 (14.2-18.0) | 20.6 (14.1-27.0) | 16.4 (13.1-19.6) |
| **BMI** | | | | | | | | |
| Thin (>=18.5) | 1.7 (0.5-2.9) | 1.3 (0.2-2.3) | 1.6 (0-4.6) | 0.1 (0-0.2) | 0.6 (0-1.2) | 0.6 (0-1.1) | 0.6 (0-1.3) | 0.3 (0-0.8) |
| Normal (18.5-24.99) | 40.5 (35.4-45.7) | 29.6 (25.7-33.6) | 35.1 (27.3-42.9) | 26.3 (21.5-31.1) | 29.9 (26.6-33.1) | 23.1 (20.3-25.9) | 23.5 (17.3-29.8) | 21.4 (17.7-25.1) |
| Overweight (25-29.99) | 37.3 (32.9-41.7) | 34.2 (30.1-38.3) | 40.8 (33.4-48.1) | 36.7 (31.6-41.8) | 38.9 (35.5-42.3) | 35.6 (32.0-39.2) | 44.5 (36.0-53.0) | 33.1 (28.3-38.0) |
| Obesity (>=30) | 20.4 (17.1-23.8) | 34.8 (30.9-38.8) | 22.5 (16.5-28.5) | 36.9 (32.5-41.4) | 30.6 (27.4-33.8) | 40.7 (37.9-43.5) | 31.4 (24.4-38.5) | 45.1 (40.7-49.5) |
| White-collar (vs. blue-collar) | 30.8 (26.6-35.0) | 24.4 (21.6-27.2) | 25.9 (19.8-32.0) | 28.8 (24.5-33.1) | 31.1 (27.5-34.6) | 25.9 (23.5-28.3) | 39.3 (30.8-47.8) | 28.8 (25.2-32.3) |
| **Gross weekly income level** | | | | | | | | |
| 1st-lowest | 12.7 (9.9-15.5) | 7.2 (5.1-9.2) | 6.9 (2.7-11.1) | 4.7 (2.7-6.7) | 6.3 (4.3-8.3) | 5.5 (4.0-6.9) | 8.7 (4.6-12.7) | 6.2 (4.4-7.9) |
| 2nd | 13.1 (10.1-16.0) | 13.1 (10.6-15.7) | 8.9 (4.5-13.2) | 14.1 (10.7-17.4) | 10.0 (7.7-12.3) | 13.3 (11.2-15.4) | 16.0 (9.1-22.9) | 15.7 (12.2-19.1) |
| 3rd | 22.1 (18.4-25.7) | 24.6 (21.2-28.1) | 20.9 (14.1-27.8) | 22.4 (18.0-26.7) | 22.3 (18.8-25.8) | 21.8 (18.6-25.1) | 19.9 (14.3-25.6) | 25.0 (20.5-29.6) |
| 4th | 30.9 (27.1-34.7) | 27.9 (24.5-31.2) | 30.6 (22.7-38.4) | 25.6 (21.1-30.0) | 28.0 (23.2-32.8) | 26.9 (24.1-29.7) | 27.6 (19.8-35.4) | 27.0 (22.7-31.4) |
| 5th-highest | 21.2 (18.1-24.3) | 27.2 (23.7-30.7) | 32.8 (25.5-40.0) | 33.3 (28.8-37.9) | 33.4 (29.3-37.5) | 32.5 (29.5-35.4) | 27.8 (21.2-34.4) | 26.1 (22.3-30.0) |

MM=multimorbidity. CVD=cardiovascular disease. BMI=Body mass index. Values are % (95%CI). Sample size (n) are showed with crude data, percentage and mean times of visits are estimated with weighting strategy. The sample size of working participants was 10,363.

**Table 2.** (continue)

| | Osteoporosis | | Diabetes | | Kidney | | Mental | |
|---|---|---|---|---|---|---|---|---|
| | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** |
| | **n=21** | **n=183** | **n=191** | **n=617** | **n=22** | **n=126** | **n=410** | **n=976** |
| Male (vs. female) | 36.2 (10.2-62.2) | 26.4 (18.1-34.6) | 47.6 (38.2-57.1) | 54.8 (50.1-59.5) | 40.6 (8.9-72.2) | 43.5 (31.8-55.3) | 53.2 (47.0-59.5) | 43.0 (39.0-47.0) |
| **Age** | | | | | | | | |
| 15-24 yrs. | 6.8 (0-20.9) | 0.1 (0-0.3) | 8.2 (2.3-14.2) | 6.0 (2.8-9.3) | 23.9 (0-60.6) | 3.8 (0.3-7.3) | 25.6 (18.9-32.4) | 9.6 (6.8-12.3) |
| 25-34 yrs. | - | 4.4 (0-9.4) | 20.5 (13.9-27.0) | 8.0 (5.1-11.0) | 9.9 (0-29.0) | 7.7 (2.9-12.5) | 24.2 (18.6-29.8) | 17.9 (15.1-20.8) |
| 35-44 yrs. | 40.0 (0-66.3) | 8.1 (2.0-14.2) | 26.9 (18.1-35.6) | 19.5 (15.1-23.9) | 28.0 (0.6-55.4) | 12.3 (4.9-19.7) | 26.6 (20.6-32.6) | 23.3 (19.9-26.7) |
| 45-54 yrs. | 15.6 (0-32.7) | 27.4 (19.0-35.8) | 24.4 (15.9-32.8) | 29.6 (25.4-33.8) | 23.3 (0-51.1) | 43.8 (31.7-55.9) | 14.1 (10.0-18.3) | 27.2 (23.2-31.1) |
| 55-64 yrs. | 25.4 (0.9-49.9) | 48.4 (38.4-58.4) | 17.4 (8.6-26.2) | 28.3 (23.9-32.7) | 15.0 (0-33.9) | 21.6 (13.7-29.6) | 8.2 (5.1-11.4) | 17.7 (14.5-20.8) |
| 65+ yrs. | 12.2 (0-28.9) | 11.6 (6.4-16.9) | 2.7 (0.6-4.7) | 8.5 (6.1-11.0) | - | 10.8 (4.3-17.3) | 1.2 (0-2.5) | 4.3 (2.5-6.2) |
| Married (vs. unmarried) | 33.5 (8.4-58.6) | 62.8 (55.4-70.3) | 65.7 (57.3-74.1) | 58.7 (53.3-64.1) | 34.3 (3.8-64.7) | 60.4 (49.2-71.7) | 33.3 (27.4-39.1) | 49.6 (45.1-54.1) |
| Has educational attainment (vs. do not has) | 53.1 (24.8-81.5) | 71.8 (63.0-80.6) | 72.1 (64.3-80.0) | 69.7 (64.4-75.1) | 82.3 (57.7-100) | 73.8 (63.6-84.1) | 65.3 (58.9-71.8) | 70.7 (66.6-74.8) |
| Current smoker (vs. non-smoker) | 3.9 (0-12.0) | 16.4 (10.1-22.7) | 21.7 (14.2-29.1) | 15.9 (12.3-19.4) | 17.4 (0-42.7) | 12.8 (5.7-19.9) | 30.0 (24.2-35.7) | 26.4 (22.5-30.3) |
| **BMI** | | | | | | | | |
| Thin (>=18.5) | - | 1.7 (0-5.2) | - | 0.4 (0-1.2) | - | - | 2.1 (0.2-3.9) | 1.0 (0.1-1.8) |
| Normal (18.5-24.99) | 64.0 (29.2-98.7) | 35.1 (24.2-45.9) | 31.1 (22.3-40.0) | 11.2 (7.6-14.8) | 51.5 (12.2-90.9) | 25.3 (14.5-36.1) | 41.4 (34.5-48.2) | 28.0 (23.8-32.3) |
| Overweight (25-29.99) | 36.0 (1.3-70.8) | 38.6 (26.2-51.1) | 34.3 (24.7-43.9) | 34.2 (28.5-39.9) | 14.1 (0-31.5) | 34.9 (23.7-46.0) | 27.6 (22.3-32.9) | 34.1 (29.1-39.1) |
| Obesity (>=30) | - | 24.6 (15.3-33.9) | 34.6 (25.0-44.2) | 54.3 (48.7-59.9) | 34.4 (0-70.4) | 39.8 (26.9-52.8) | 29.0 (22.1-35.8) | 36.9 (32.3-41.5) |
| White-collar (vs. blue-collar) | 20.2 (0.5-40.0) | 16.4 (8.8-24.0) | 28.5 (20.7-36.4) | 28.0 (23.5-32.5) | 24.0 (0-53.2) | 28.4 (19.8-36.9) | 30.8 (23.6-38.0) | 26.8 (23.4-30.2) |
| **Gross weekly income level** | | | | | | | | |
| 1st-lowest | 3.8 (0-11.7) | 7.8 (2.1-13.6) | 10.7 (2.8-18.5) | 8.4 (5.0-11.8) | 16.0 (0-42.0) | 7.7 (1.4-14.0) | 13.4 (7.9-18.8) | 7.2 (5.0-9.5) |
| 2nd | 4.9 (0-15.3) | 17.2 (10.4-24.0) | 10.3 (4.2-16.3) | 12.8 (8.9-16.7) | 46.7 (3.2-90.2) | 16.3 (6.9-25.8) | 14.3 (8.8-19.7) | 14.1 (10.8-17.4) |
| 3rd | 32.6 (3.1-62.1) | 23.4 (14.2-32.6) | 25.5 (16.1-34.9) | 23.8 (18.6-28.9) | 5.9 (0-16.7) | 27.0 (16.4-37.7) | 27.3 (20.7-33.9) | 30.1 (26.3-33.8) |
| 4th | 42.9 (10.7-75.1) | 27.3 (18.9-35.7) | 28.0 (18.8-37.1) | 27.7 (23.0-32.3) | 22.6 (0-49.8) | 15.2 (8.1-22.2) | 25.2 (19.3-31.0) | 25.6 (21.9-29.3) |
| 5th-highest | 15.8 (0-37.7) | 24.2 (16.2-32.3) | 25.6 (18.1-33.1) | 27.4 (22.5-32.3) | 8.7 (0-22.4) | 33.7 (21.3-46.2) | 19.9 (14.6-25.2) | 23.0 (19.6-26.5) |

**Table 4-3.** 12-month disease-specific healthcare service utilization of GPs, specialists and other health professionals by disease status (alone and coexisting with other conditions).

| | Asthma | | Cancer | | CVD | | Arthritis | |
|---|---|---|---|---|---|---|---|---|
| | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** |
| | **n=975** | **n=1175** | **n=304** | **n=766** | **n=1258** | **n=1917** | **n=325** | **n=970** |
| **Disease-specific** | | | | | | | | |
| GP visits | | | | | | | | |
| 0 visit | 59.0 (52.6-65.4) | 56.0 (50.2-61.8) | 36.7 (3.1-70.2) | 31.3 (17.0-45.7) | 37.4 (32.3-42.5) | 36.0 (31.1-40.9) | 62.7 (53.2-72.2) | 57.8 (52.6-63.1) |
| 1 visit | 24.4 (18.4-30.3) | 22.1 (17.7-26.4) | 23.3 (3.8-42.9) | 32.9 (18.8-47.1) | 20.0 (15.8-24.1) | 19.7 (16.5-22.9) | 27.5 (18.0-36.9) | 21.2 (16.8-25.5) |
| 2 visits | 7.5 (4.5-10.5) | 11.7 (8.3-15.1) | 8.6 (0-27.3) | 21.0 (7.6-34.4) | 25.0 (20.5-29.5) | 20.0 (16.1-23.8) | 6.4 (2.2-10.5) | 9.8 (6.8-12.7) |
| 3 visits | 6.2 (3.3-9.1) | 4.2 (2.1-6.3) | 0.6 (0-2.0) | 5.0 (0-11.1) | 6.3 (3.6-9.0) | 6.9 (4.6-9.2) | 1.8 (0-3.7) | 4.5 (2.7-6.3) |
| 4+ visits | 2.9 (1.1-4.7) | 6.0 (3.5-8.6) | 30.8 (0-65.9) | 9.8 (1.2-18.4) | 11.4 (7.9-14.9) | 17.4 (14.1-20.6) | 1.7 (0.1-3.3) | 6.8 (4.9-8.7) |
| Specialist visits | | | | | | | | |
| 0 visit | 98.0 (96.7-99.3) | 96.6 (94.8-98.3) | 45.9 (13.3-78.6) | 42.9 (24.9-61.0) | 87.3 (84.0-90.6) | 85.0 (81.9-88.1) | 80.2 (71.9-88.6) | 85.8 (82.8-88.9) |
| 1 visit | 1.2 (0.1-2.2) | 1.8 (0.6-3.0) | 19.4 (0-39.6) | 17.2 (1.2-33.2) | 7.9 (5.5-10.3) | 8.8 (6.2-11.4) | 6.4 (1.8-10.9) | 7.3 (5.0-9.6) |
| 2+ visits | 0.8 (0-1.7) | 1.6 (0.3-3.0) | 34.7 (7.9-61.5) | 39.8 (24.0-55.7) | 4.8 (2.3-7.3) | 6.2 (4.2-8.2) | 13.4 (6.4-20.4) | 6.9 (4.6-9.1) |
| Visit other HP at least once | 10.1 (6.1-14.1) | 6.1 (3.9-8.3) | 24.2 (0-53.0) | 26.6 (13.0-40.2) | 4.4 (2.4-6.3) | 9.9 (7.9-12.0) | 17.4 (10.6-24.3) | 20.1 (16.4-23.8) |
| | **Osteoporosis** | | **Diabetes** | | **Kidney** | | **Mental** | |
| | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** | **Only** | **In MM** |
| | **n=21** | **n=183** | **n=191** | **n=617** | **n=22** | **n=126** | **n=410** | **n=976** |
| **Disease-specific HSU** | | | | | | | | |
| GP visits | | | | | | | | |
| 0 visit | 57.3 (29.3-85.3) | 45.5 (36.2-54.8) | 19.9 (5.2-34.5) | 18.1 (9.9-26.3) | 42.1 (0-100) | 62.1 (40.4-83.8) | 37.3 (28.5-46.0) | 38.6 (33.5-43.7) |
| 1 visit | 33.2 (6.4-60.1) | 28.6 (19.6-37.5) | 19.0 (6.5-31.5) | 17.9 (11.7-24.2) | 33.4 (0-89.3) | 12.8 (0-26.2) | 24.6 (15.2-33.9) | 18.9 (14.5-23.3) |
| 2 visits | 9.4 (0-29.3) | 16.7 (6.8-26.6) | 23.3 (7.6-38.9) | 26.2 (17.3-35.1) | - | 9.6 (0-22.5) | 16.6 (9.9-23.4) | 14.6 (10.7-18.5) |
| 3 visits | - | 3.6 (0-7.3) | 11.7 (0-25.4) | 10.0 (5.0-14.9) | 24.5 (0-81.5) | 1.8 (0-5.5) | 8.7 (5.0-16.8) | 9.9 (6.8-13.0) |
| 4+ visits | - | 5.6 (1.0-10.3) | 26.1 (8.9-43.3) | 27.8 (20.3-35.3) | - | 13.7 (1.3-26.1) | 12.9 (6.7-19.0) | 18.0 (14.7-21.2) |
| Specialist visits | | | | | | | | |
| 0 visit | 100 (100-100) | 86.5 (79.2-93.8) | 60.7 (44.4-76.9) | 76.7 (68.7-84.8) | 59.2 (0-100) | 49.4 (30.9-68.0) | 80.4 (73.3-87.4) | 80.0 (76.2-83.6) |
| 1 visit | - | 6.1 (1.8-10.4) | 17.1 (2.2-32.0) | 7.2 (2.8-11.5) | 40.8 (0-100) | 20.1 (0.4-39.9) | 4.3 (0.9-7.6) | 3.9 (2.3-5.6) |
| 2+ visits | - | 7.4 (1.8-12.9) | 22.2 (9.1-35.3) | 16.1 (9.1-23.1) | - | 30.4 (14.2-46.6) | 15.3 (9.0-21.7) | 16.2 (12.4-19.9) |
| Visit other HP at least once | 10.4 (0-22.3) | 13.4 (6.6-20.2) | 42.8 (26.2-59.3) | 38.1 (30.0-46.3) | - | 2.5 (0-5.8) | 28.5 (20.9-36.1) | 26.5 (22.8-30.3) |

GP=general practitioner. HP=health professional. MM=multimorbidity. CVD=cardiovascular disease. HSU=healthcare service utilization. Values are % (95%CI). The sample size of working participants was 10,363.

**Table 4-4.** Multivariate analysis of disease-specific healthcare service utilization of GPs, specialists and other health professionals associated with employees with specific condition only compared to those with specific condition coexisting with other chronic conditions.

| | **GPs** | | **specialists** | | **Other HPs** | |
|---|---|---|---|---|---|---|
| | **RR (95% CI)** | ***p*** | **RR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| **Asthma** | N=1087 | | N=1166 | | N=1171 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | 1.0 (0.7,1.2) | 0.823 | 0.7 (0.2,2.6) | 0.634 | 0.7 (0.4,1.2) | 0.160 |
| **Cancer** | N=89 | | N=90 | | N=112 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | 0.7 (0.1,1.3) | 0.365 | 1.2 (0.5,2.9) | 0.749 | 1.4 (0.1,14.0) | 0.796 |
| **CVD[a]** | N=1302 | | N=1718 | | N=1750 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | 1.1 (0.8,1.2) | 0.680 | **1.6 (1.1,2.5)** | ***0.03*** | **2.5 (1.5,4.0)** | ***<0.001*** |
| **Arthritis[b]** | N=835 | | N=1031 | | N=1056 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | **1.7 (1.1,2.2)** | ***<0.001*** | 0.9 (0.4,1.8) | 0.728 | 1.2 (0.7,2.1) | 0.453 |
| **Diabetes** | N=268 | | N=317 | | N=329 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | 0.9 (0.5,1.2) | 0.540 | 1.0 (0.4,2.3) | 0.999 | 0.9 (0.4,2.0) | 0.796 |
| **Mental disorder** | N=814 | | N=873 | | N=935 | |
| Only | 1.0 | | 1.0 | | 1.0 | |
| In MM | 1.2 (0.9,1.5) | 0.262 | 0.5 (0.8,2.8) | 0.163 | 1.0 (0.7,1.4) | 0.839 |

GP=general practitioner. HP=health professional. MM=multimorbidity. CVD=cardiovascular disease. Poisson regression models were used for the relationship between the number of visits with GP, specialists and the multimorbidity status. Logistic regression models were used for the relationship between the number of visits with other HP and the multimorbidity status. Significant estimates are typed in bold font ($p<0.05$). Sample size (n) are showed with crude data, rate ratios (RR) and odds ratios (OR) are estimated with weighting strategy. The sample size of working participants was 10,363.

All models adjusted for age and sex, models additionally adjusted for: a: BMI; b: educational attainment and BMI.

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# Chapter 6. A Systematic Review of Cost-of-Illness Studies of Multimorbidity

## 6.1 Preface

Previous chapters have focused on the negative associations of multimorbidity with a range of health outcomes including health-related quality of life, healthcare service utility and lost productivity. In this chapter, we turn to exploring the costs of multimorbidity in existing literature. This work is important, as the economic burden of multimorbidity is considerable and continues to raise, whereas there is no summary evidence of the economic burden of multimorbidity. Therefore, this chapter conducted a systematic review aiming to analyse the methods of cost-of-illness (COI) studies on multimorbidity and summarize the economic outcomes of multimorbidity, to help us outline the current researches on multimorbidity, identify the gaps in order to improve and shape future COI studies on multimorbidity.

The text that follows is included in a manuscript that has been accepted by Applied Health Economics and Health Policy on 14 Aug 2017.

## 6.2 Introduction

The term multimorbidity refers to the presence of multiple concurrent chronic health conditions in one individual without an index disease [1]. Regardless of the specific definition of multimorbidity adopted, it is common [2], particularly in the elderly with prevalence estimates of 65-98% for those aged >65 years [3-5]. Additionally, a growing body of evidence has indicated an increasing prevalence of multimorbidity [6]. In the Netherlands, Uijen and van de Lisdonk found that the prevalence of people with two or more chronic health conditions increased from 12.3% to 20.5% in primary care from 1985 to 2005 [7]. In the United States, Ward found that the prevalence of multimorbidity increased from 21.8% in 2001 to 25.5% in 2012 using the data from a national household survey [8, 9].

Multimorbidity is one of the most problematic "chronic health conditions" [10] because of the escalating prevalence and its far-reaching health consequences. Multimorbidity can have a drastic and lifetime impact, as it is unlikely to be cured. Additionally, compared to single health conditions, multimorbidity has been related to poorer health-related quality of life [11, 12], higher health service utilization [13], and negative occupational consequences [14], such as productivity loss due to presenteeism (e.g., 'continuing to work while sick') and absenteeism. Moreover, healthcare resource consumption is expected to increase not only because of the accumulation of chronic health conditions but also because of interactions and synergies among health conditions present within an individual [15]. Given the concurrent changes in epidemiology, the use of resources and morbidity-related costs of multimorbid conditions are likely to undergo enormous changes as well, especially since uniform definition and measure of multimorbidity have been lacking.

Some researchers have begun to summarize the associations of multimorbidity and costs. Lehnert et al. reviewed the literature in 2011 which was restricted to studies of older adults only [16]. Sambamoorthi et al. conducted a narrative expert review which does not meet the criteria for a systematic review, i.e. did not report use of systematic review methodology, did not describe a study protocol and therefore was not registered on Prospero, did not include a standardised assessment of study quality, and did not follow guidelines for reporting systematic reviews (e.g. PRISMA) [17]. Our review meets all of these criteria and we believe it presents an important and distinct contribution to this field. Another advantage of this review was providing the breakdown of costs. The aim of this study was two-fold: we first compiled a general description of COI methods, and we subsequently systematically reviewed studies on the costs of multimorbidity, analyzing the different methods used, summarizing their findings on the economic impact of multimorbidity and evaluating the quality of the included COI studies.

## 6.3 Methods

### 6.3.1 Literature review

A literature search was performed in the following electronic databases: PROSPERO, Cochrane Library (including the HTA Database, DARE and Cochrane Database of Systematic Reviews), Health Economic Evaluations databases (including the NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED)), National Institute for Health and Care Excellence (NICE) Evidence Services, Google Scholar, Scopus, and PubMed. The search strategy combined key words related to multimorbidity, comorbidity and multiple chronic health conditions. The search was restricted to papers written in English and published since 2000 up to October 2016. The inclusion criteria were peer-reviewed COI studies (including cross-sectional, cohort and modeling studies); the exclusion criterion was studies focusing on an index disease. The main difference between comorbidity and multimorbidity was whether an index disease was specified or not. Calculating the costs without distinguishing those two situations may lead to an underestimation of the burden of multimorbidity. As in “comorbidity”, allied treatments of the dominant disease might also apply to the triggered secondary diseases, while in “multimorbidity”, each disease receives relatively independent treatments. Therefore, we included “comorbidity” in the search terms primarily because of the interchangeable use of the terms “comorbidity” and “multimorbidity” in the literature. Then, during the article screening stage, studies were excluded if they focused on “an index disease”. Figure 1 illustrates the literature search and selection process and presents the reasons for study exclusion. As an example, the search strategy for PubMed is shown below.

(((multimorbidity[Title/Abstract]) OR (multi-morbidity[Title/Abstract]) OR (comorbidity[MeSH Terms]) OR (co-morbidity[Title/Abstract]) OR ((multiple[Title/Abstract]) AND (chronic[Title/Abstract] OR long-term[Title/Abstract] OR "long term"[Title/Abstract]) AND (illnesses[Title/Abstract] OR diseases[Title/Abstract] OR conditions[Title/Abstract]))) AND ((forecasting[MeSH Terms]) OR (health expenditures[MeSH Terms]) OR (spending[Title/Abstract]) OR (costs and cost analysis[MeSH Terms]) OR (cost-of-illness[Title/Abstract]) OR (cost of illness[Title/Abstract])) AND English[Language] AND ("2000"[Date - Publication] : "3000"[Date - Publication])) NOT (letter[Publication Type] OR news[Publication Type] OR editorial[Publication Type] OR “newspaper article”[Publication Type] OR comment[Publication Type]).

All titles and abstracts were screened by two independent reviewers (LLW and LS), after which the full texts of all potentially eligible papers were obtained and screened by the same two reviewers. For any disagreement, the abstract was set aside for further evaluation. After a consensus was reached on the final sample of papers, the primary reviewer (LLW) screened the reference lists of the included papers for additional papers that fulfilled the inclusion criteria. This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].

Formal international guidelines for quality analyses of COI studies are lacking; therefore, relevant information was extracted referring to the British Medical Journal Checklist [19] for economic submissions and was adapted for COI studies by Molinier et al. [20]. Equal weight was assigned to each item of the checklist, and the final score was the sum of the 10 individual items. The two reviewers assessed each study separately. If there was disagreement between two reviewers at this stage, the paper was discussed with reference to the aforementioned COI study checklist until agreement was reached.

This systematic review summarized the results referring to the items of COI methods, which have been described elsewhere [19-21]. The items included the definition of multimorbidity, the epidemiological approach, the perspective of the study and the type of costs assessed, resource consumption and unit costs, and sensitivity analyses (dimensions shown in Table 6-1 and Table 6-2).

### 6.3.2 Presentation of results

Investigating subgroup heterogeneity in COI estimates represents an area for future research [22]. Therefore, the included studies had to be stratified and presented by different components of costs, with clear explanations of the groups. To make the costs comparable, cost estimates were all converted to USD ($), according to the 2016 exchange rate for each study and each currency, with adjustments over time based on the Consumer Price Index (CPI) for the original currency. Costs were reported as average annual costs (per-capita costs) unless stated otherwise, because the total costs

reported in the different studies varied depending on the included sample sizes. The results were synthesized descriptively.

## 6.4 Results

A total of 7,249 studies were identified from the PubMed and Scopus literature search. After the titles, abstracts and full text were screened, 19 studies remained. Then, we incorporated three studies from other databases that were not identified from PubMed and Scopus. With these 22 studies, we screened the references and identified four studies that had not been identified in our literature search. Finally, twenty-six studies met our criteria (shown in Tables 6-1 to 6-3). The years of valuation ranged from 1996 to 2013. Thirteen studies were conducted in the United States [3, 23-34], seven in Europe [13, 35-40], two in Australia [41, 42], one each from Canada [43], Singapore [44] and Taiwan [45], and two in middle- or low-income regions [40, 46]. Overall, twenty studies used a prevalence approach [3, 13, 23-28, 30-32, 35, 37-42, 44, 46], seven used an incidence approach [27, 29, 33, 34, 36, 43, 45], and only one used an economic model to estimate the lifetime costs of multimorbidity [36]. The studies analyzed samples ranging in size from 1,252 to 292 million [28]. Twenty-five studies specified the age range of the sample [26]. Twenty-one studies calculated estimates in a population 65 years and older [3, 13, 23-25, 27, 28, 30-32, 35-42, 44-46], eight studies included people under 18 years old [23-25, 28, 30, 36, 38, 45], and three studies were conducted in children only [33, 34, 43]. The average annual cost of multimorbidity per capita ranged from $49 [40] to $252,313 [33], showing significant variation by study. Additionally, out-of-pocket (OOP) expenditures ranged from $49 [40] to $6,858 [27], which was lower than public insurance costs. Children with three or more life-threatening complex chronic conditions in their last year of life had the highest costs ($252,313) [33].

### *Identifying multimorbidity*

In total, fourteen studies provided the same, clear definition of multimorbidity, i.e., the ≥2 simple count method [13, 23, 29-32, 35, 37-41, 44, 46]. Twelve studies estimated the costs by number, including five "organ system" and seven "health condition or symptom" studies, although they did not refer to the term "multimorbidity". For other definitions of multimorbidity, COI information was very limited. Only four studies accounted for

the severity of health conditions when measuring multimorbidity; two of them used the Cumulative Illness Rating Scale (CIRS) [35, 37]; the Clinical Risk Groups (CRG) model [36] and Rx-defined morbidity groups (Rx-MG) [45] were each used only once. The number of health conditions included when identifying multimorbidity ranged from 4 [32] to 259 [23, 26, 29].

### *Epidemiological approach*

Six studies followed an incidence-based approach [27, 29, 33, 34, 36, 43, 45], and twenty studies calculated prevalence-based healthcare costs [3, 13, 23-28, 30-32, 35, 37-42, 44, 46]. Lifetime costs were estimated in only one study [36], and unfortunately, specific multimorbidity-related costs were unavailable.

### *Perspective of the analysis and costs assessed*

Three perspectives were included: eighteen studies were from the payer's perspective [3, 23-31, 34, 36, 39-42, 45, 46], six were from healthcare providers' perspective [13, 32, 33, 35, 38, 43], and two used the societal perspective [37, 44]. However, both of the studies from the societal perspective defined costs as including only healthcare and social care costs. Twelve studies included both medical and non-medical expenditures when quantifying direct costs [3, 23, 24, 27, 28, 31, 32, 37, 40-42, 44].

### *Estimating resource consumption*

Three approaches can be used to estimate resource consumption: bottom-up, top-down and econometric [47]. While the top-down approach typically requires cost data as well as relative risks to calculate population-attributable fractions, the bottom-up approach often requires data from multiple sources, and the econometric approach often requires only a single dataset [47]. Sixteen studies gathered data on resource consumption from different departments (bottom-up approach) [3, 13, 25, 26, 29-38, 43, 45]. One used a combined bottom-up and top-down approach [35]. Ten studies extracted costs from the single database, called an econometric approach [23, 24, 27, 28, 39-42, 44, 46]. The follow-up periods included lifetime follow-up in a study that adopted an

incidence-based approach [36], six years in one study [45], four years in three studies [29, 33, 34] and two years in one study [43].

### *Valuation of unit costs*

*Sources of cost estimations*

Most American studies calculated costs from Medicare payments and the Medical Expenditure Panel Survey (MEPS), which provided national, continuous and comparable estimates over time. An Irish study used data from primary care consultations and outpatient and inpatient visits extracted from family practices [13]. One study quantified indirect costs [44]. Four studies did not provide the unit costs [25, 36, 38], and one study reported the unit incremental cost only [37].

*Discounting costs*

Studies with time horizon less than one or two years did not normally discount costs. In all included studies in this review, costs were not discounted, even in the longitudinal studies with more than a two-year follow-up.

### *Sensitivity analysis*

None of the studies analyzed or discussed the variables that had a significant impact on cost estimates.

### *Presentation of results*

The results were clearly presented in most studies and were mainly well explained and consistently reported in relation to the methods adopted. Three studies did not differentiate costs. Based on the key methodological points, a checklist of questions was used with full explanations given for clarity (Table 6-3). For fourteen studies, the answer to seven of ten questions was "yes", and all the studies were scored "no" on question 9 "Were the major assumptions tested in a sensitivity analysis?" Questions 3 "Were direct/indirect costs sufficiently disaggregated?" and 7 "Were unit costs appropriately valued?" received fewer "yes" answers than the other questions. In one

American study [24], the costs were sufficiently disaggregated only for single conditions, and the costs of multimorbidity were presented only as additional or supplementary information.

## 6.5 Discussions

We systematically reviewed 26 COI studies on multimorbidity without restricting the studies to any specific definition of multimorbidity, and this broad inclusion contributed to a comprehensive understanding of multimorbidity and its economic burden. The costs of multimorbidity ranged from $49 [40] to $252,313 [33] annual per capita and increased according to the level of multimorbidity within each study. We found a relative paucity of data on the costs of multimorbidity, but the available data still provided valuable information for us to better elucidate the current magnitude of the economic burden of multimorbidity. Methods were highly heterogeneous producing a wide range of COI estimates. Even at the lower bounds, these costs were substantial.

***Costly multimorbidity***

The proportion of costs due to multimorbidity in relation to the total costs ranged from 3.4 to 97.8%. Most (n=18) estimates were 60% and above. One study with an extraordinarily low estimate (3.4%) [42], which seemed inconsistent with the other studies, only evaluated three-month cases of out-of-pocket (OOP) expenditures in Australia. The conditions included in the study were all chronic, which required ongoing treatment [48], and the short duration of the study may not have reflected all incurred costs.

The highest costs of multimorbidity per person occurred in the last year of life among children with life-threatening conditions ($252,313) [33]. The costs in all three studies with young respondents ranged from $8,551 [34] to $252,313 [33] and did not include direct non-medical or indirect costs. Although the childhood prevalence estimates of chronic health conditions ranged from 0.22% to 44% [49], which was much lower than the 12.9% to 95.1% prevalence of multimorbidity in the broader age groups [50], multimorbid children and their families still faced substantial financial pressure.

Moreover, the included studies indicated a persistence of high costs in the following years.

***Heterogeneity of multimorbidity COI studies***

Three relevant perspectives of the costs of multimorbidity were included. The societal perspective, including care costs, was used in two studies, but they did not account for the costs of productivity loss due to multimorbidity [51], including presenteeism, absenteeism, premature retirement and death, which are responsible for a substantial proportion of the financial burden [52]. Information about productivity loss, premature retirement and death could be derived from the working population. Only one Australian study in this review was conducted among working-age adults and included those who were not in the workforce [29]. Unemployed populations are more likely to have more chronic conditions than employed groups [51]. However, that study did not estimate productivity loss, which could have been addressed with the available data.

Six studies adopted a cohort study design, with follow-up periods ranging from two to six years. The remaining twenty studies used cross-sectional data, which reflect only the time of data collection and are limited in their ability to draw valid conclusions about associations or possible causality [53]. Compared to other reviews of COI studies on a specific single disease, this review on multimorbidity included fewer cohort studies [54]. Data collection over a long period of time is difficult and time- and cost-intensive; however, modeling designs could compensate for these challenges [55]. In this review, only Carreras et al. simulated individual costs until death using a stationary Markov chain under the assumption that transition probabilities were constant [36]. This approach was not consistent with the nature of chronic conditions, in which health states change dynamically, and modeling of chronic conditions should consider this difference [55]. However, the lifetime multimorbidity costs could be reasonably predicted in this regional study.

Several studies did not fully describe their methods and were thus difficult to assess. This ambiguity might be due to a general lack of economic awareness in the medical journals that support economic studies. A community-based cohort ensures a more

representative patient population, but the diagnosis of this cohort may rely on self-reported data, which are certainly less precise. However, the included studies confirm multimorbidity is costly.

Given different healthcare systems, OOP payments varied across countries, but OOP expenditure of multimorbidity is always greater than that of non-multimorbidity. For example, in China, the patients with multimorbidity have higher OOP expenditure than those without multimorbidity, even among those with health insurance [40]. Findings from economic studies in different countries or regions cannot be easily generalized due to monetary issues; for example, different currencies have different purchasing power for the same product [56].

***Definitions of multimorbidity***

It is well known that there is no singular definition of multimorbidity, and the two cut-off count method is generally the most broadly accepted definition used. In this review, we found that all the COI studies that provided a definition of multimorbidity adopted only this method. Most of the studies that did not specifically define multimorbidity also presented costs by the number of multimorbid conditions. Using the same definition increased the comparability within the available COI studies.

The number of included health conditions used to identify multimorbidity ranged from 4, which were highly prevalent, disabling or expensive conditions in an American community [32], to 259, which included all conditions in clinical classification systems [29]. The costs did not increase as more conditions were included. The wide variation in severity within specific conditions [57] could produce different costs. For example, children with life-threatening conditions had the highest healthcare expenditure in this review [33].

Using a cut-off of two or more conditions, the proportional increase in cost for multimorbid compared to non-multimorbid ranged from 100% to 1500%, while from 100% to 900% when using the three cut-off count method. Nevertheless, interpreting these quantitative results is problematic because of the different approaches used. Domestic characteristics within each country or region, such as clinical practice

settings and healthcare systems, also affect resource consumption and unit costs. For example, medication costs can vary among studies because of the use of tariffs in solidarity systems, which are not comparable to free prices in private systems.

The different methodologies used to identify multimorbidity led to the wide range in expenditures reported above. The number and diversity of available studies on multimorbidity provide an insufficient scientific basis for further explorations on multimorbidity. Therefore, it is vital to improve the methodological quality of multimorbidity COI research to gain a better understanding of this common and important phenomenon. Moreover, further research is needed to clarify the costs of multimorbidity from the societal perspective.

***Limitations and strengths***

The results of this review are limited by the nature of the studies identified. The main limitation of this review is its inability to include all relevant studies. Costs were estimated in 16 countries or regions from 1996 to 2013. The large number of abstracts derived from the databases improved the sensitivity of our search strategy. The absence of a MeSH term for multimorbidity is a clear limitation. However, adding multimorbidity-related terms from previous studies to our search strategy helped circumvent this limitation. We included papers published in English only, which restricted our sample to some extent. The OOP can vary widely between countries because of different health insurance systems and types of diseases, therefore, we have only reported the range of OOP payment in different countries. Based on the fact that multimorbidity is not prevalent in the young population, the pediatric multimorbidity studies were rare, therefore, the costs of multimorbidity could not be distinguished by age and the finding of pediatric studies in this review was limited.

Moreover, the practicality of COI studies themselves in aiding policy decision-making has been debated [58, 59], and their inability to prioritize resources has been criticized as well [60, 61]. COI studies, which aim to identify and measure all costs of health condition serve a different purpose than other health economic evaluations (e.g., cost-benefit, cost-effectiveness, and cost-utility analyses), which aim to assess both costs and outcomes of the adopted intervention/policy [62-64]. However, COI

studies can provide useful information as long as they adhere to standardized and acceptable methodologies [65, 66]. Furthermore, the results of COI studies have been used by organizations such as the World Bank and the World Health Organization to estimate public, private and total national health expenditures globally [67]. Different stakeholders can utilize COI studies for different purposes [68]. For example, governments can estimate the financial impact of a disease on public budgets for resource allocation purposes, whereas pharmaceutical corporations can identify diseases with high management costs and direct research and development investments accordingly. However, caution is warranted when using COI studies; for optimal resource allocation, they should be used in combination with other thorough economic evaluations [69].

Despite these limitations, this review provides an overview of the range of estimates reported in recent decades, and the collated evidence provides a greater understanding of the COI of multimorbidity than the results provided by individual studies. Moreover, this review adds systematic evidence about the methodologies used to analyze multimorbidity costs and provides insight into the reasons for the disparate results among studies. Although multimorbidity complicates the findings of COI studies, this review can be useful for informing decisions about the prioritization of resources [70, 71], particularly when combined with other economic assessments.

## 6.6 Conclusion

Noting the substantial methodological variations between studies, multimorbidity was associated with a considerable economic burden. Although this review identified two studies estimating the costs from a societal perspective, there was a consistent theme throughout the included studies that those with multimorbidity had higher costs than those without multimorbidity. Future research should focus on improving the methods of estimating costs. A closer agreement of definition of multimorbidity is still required to allow consistent comparisons and enhance the interpretation of study findings among future studies.

**Figure 6-1.** Flowchart illustrating the search process.

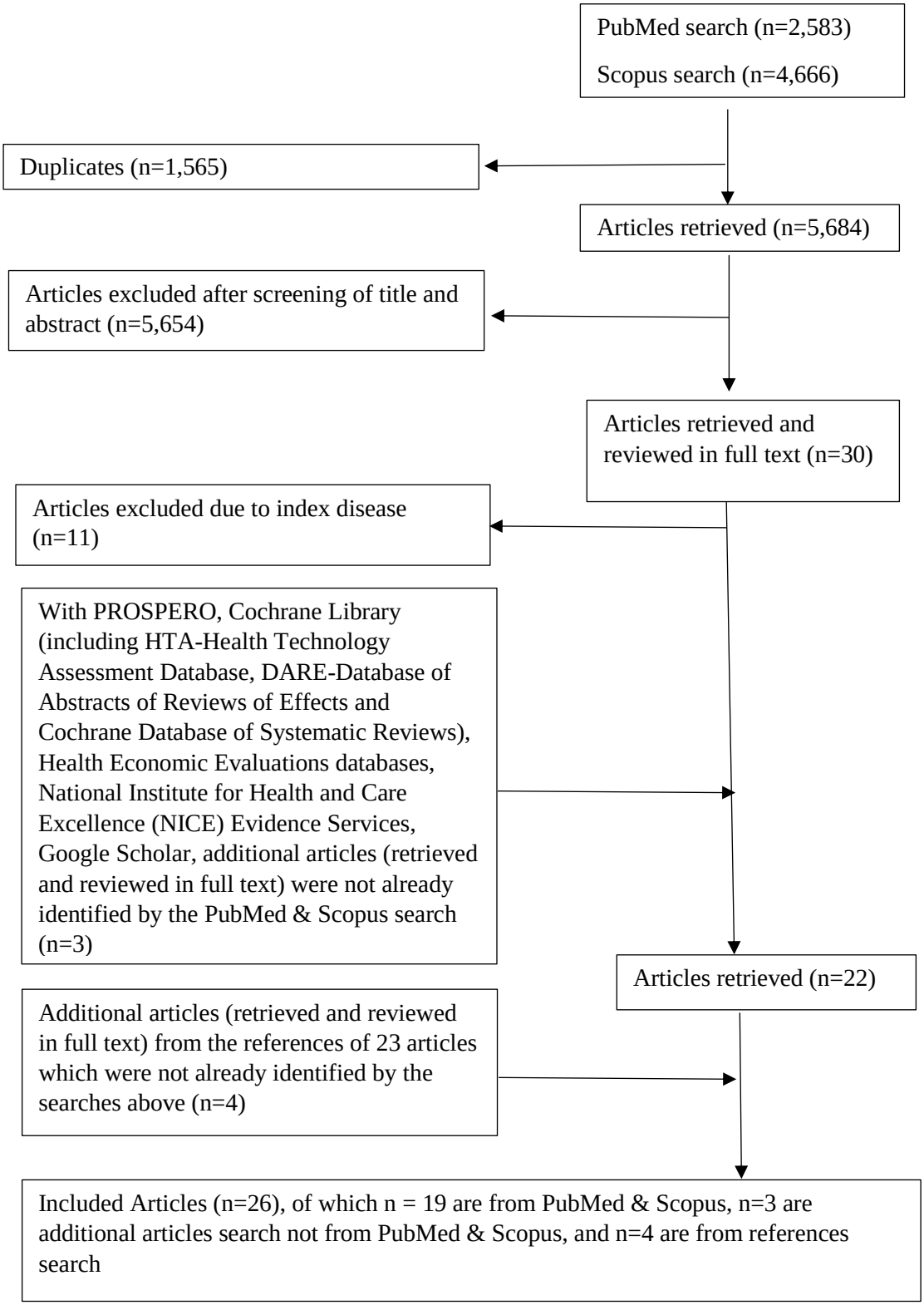

**Table 6-1.** Methodology of included cost-of-illness studies in multimorbidity.

| Study | Country | Perspective | Epidemiological approach | Study design | Year of valuation | Currency |
|---|---|---|---|---|---|---|
| Hwang et. al [23] | USA | Payer (OOP) | Prevalence | Cross-sectional | 1996 | USD |
| Garis et. al [24] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 1995 | USD |
| Wolff et. al [3] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 1999 | USD |
| Anderson et. al [25] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 1998 | USD |
| Thorpe et. al [26] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 1987 | USD |
| Thorpe et. al [26] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 1997 | USD |
| Thorpe et. al [26] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 2002 | USD |
| Schoenberg et. al [27] | USA | payer (OOP) | Prevalence/incidence | Cross-sectional | 1998 | USD |
| Schoenberg et. al [27] | USA | Payer (OOP) | Prevalence/incidence | Cross-sectional | 2002 | USD |
| Paez et. al [28] | USA | Payer (OOP) | Prevalence | Cross-sectional | 2005 | USD |
| Glynn et. al [13] | West of Ireland (national representative) | Health care providers | Prevalence | Cross-sectional | 2009 | EUR |
| Naessens et. al [29] | USA | Payer | Incidence | Cohort (4 years follow-up) | 2007 | USD |
| Nagl et. al [35] | Germany | Health care providers | Prevalence | Cross-sectional | 2010 | EUR |
| Carreras et. al [36] | the county of Baix Empordà in Catalonia (Spain) | Payer (public insurance) | Incidence | cohort (lifetime) | 2007 | EUR |
| Kuo et. al [45] | Taiwan | payer (public insurance) | Incidence | Cohort (6 years follow-up) | 2010 | USD |
| Lochner et. al [30] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 2011 | USD |
| Machlin et. al [31] | USA | Payer (public insurance) | Prevalence | Cross-sectional | 2009 | USD |
| McRae et. al [41] | Australia | Payer (public insurance) | Prevalence | Cross-sectional | 2009 | AUD |
| Heider et. al [37] | Germany | Payer (OOP) | Prevalence | Cross-sectional | 2009 | EUR |
| Orueta et. al [38] | Basque country (region in Spain/France) | Societal | Prevalence | Cross-sectional | 2011 | EUR |
| Pati et. al [46] | India | Health care providers | Prevalence | Cross-sectional | 2007 | INR |
| Bahler et. al [39] | Switzerland | Payer | Prevalence | Cross-sectional | 2013 | Swiss francs |
| Lee et. al [40] | China | Payer (OOP) | Prevalence | Cross-sectional | 2010 | CNY |
| Lee et. al [40] | Ghana | Payer (OOP) | Prevalence | Cross-sectional | 2010 | GHC |
| Lee et. al [40] | Mexico | Payer (OOP) | Prevalence | Cross-sectional | 2010 | INR |
| Lee et. al [40] | Russia | Payer (OOP) | Prevalence | Cross-sectional | 2010 | MXN |
| Lee et. al [40] | South Africa | Payer (OOP) | Prevalence | Cross-sectional | 2010 | RUB |
| Lee et. al [40] | India | payer (OOP) | Prevalence | Cross-sectional | 2010 | ZAR |
| Meraya et. al [32] | USA | health care providers & payer | Prevalence | Cross-sectional | 2011 | USD |
| Picco et. al [44] | Singapore | societal | Prevalence | Cross-sectional | 2013 | SGD |
| Carpenter et. al [42] | Australia | payer (OOP) | Prevalence | Cross-sectional | 2009 | USD |
| Cohen et. al [43] | Canada | health care providers | Incidence | Cohort (2 years follow-up) | 2005-2007 | CAD |
| Ananth et. al [33] | USA | health care providers | Incidence | Cohort (4 years follow-up) | 2012 | USD |
| Zhong et. al [34] | USA | payer (public insurance) | Incidence | Cohort (4 years follow-up) | 2004 | USD |

OOP, out-of-pocket; USA, United States of America; USD, United States Dollar; EUR, Euro; AUD, Australian Dollar; INR, Indian Rupee; CNY, Chinese Yuan; GHC, Ghana Cedi; MXN, Mexican Peso; RUB, Russian Rouble; ZAR, South African Rand; SGD, Singapore Dollar; CAD, Canadian Dollar.

**Table 6-2.** The definition, measure, costs of multimorbidity.

| Study | Definition of MM | Measure of MM | Number of included conditions | Age range (y.o.) | Prevalence of MM (%) | %(MM) of total costs | Direct costs | | Indirect costs | Average costs of MM ($)* | | MM/non-MM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Direct medical costs | Direct non-medical costs | | MM2+ | MM3+ | MM2+ | MM3+ |
| Hwang et. al [23] | MM2+ | Count | 259 | 0-80+ | 17.0 | 38.1 | yes | no | no | 1387 | 1733.0 | 3 | 3 |
| Garis et. al [24] | NS | Count | 9 | 0+ | NA | NA | yes | yes | no | 7938 | NA | NA | NA |
| Wolff et. al [3] | NS | ACG | 3493 | 65+ | 65(MM2+)/43(MM3+) | 95.3 | yes | yes | no | 10627 | 14276.0 | 11 | 10 |
| Anderson et. al [25] | NS | Count | NS | 0+ | NA | NA | yes | no | no | NA | NA | NA | NA |
| Thorpe et. al [26] | NS | Count | 259 | NS | 76.4 | 92.2 | yes | no | no | 13330 | 14989.8 | 6 | 3 |
| Thorpe et. al [26] | NS | Count | 259 | NS | 80.5 | 95.1 | yes | no | no | 10950 | 12158.8 | 5 | 4 |
| Thorpe et. al [26] | NS | Count | 259 | NS | 86.2 | 97.2 | yes | no | no | 11666 | 12864.0 | 6 | 5 |
| Schoenberg et. al [27] | NS | Count | 8 | 65+ | 58.1 | 70.6 | yes | yes | no | 3858 | 4109.0 | 2 | 2 |
| Schoenberg et. al [27] | NS | Count | 8 | 65+ | 70.4 | 78.6 | yes | yes | no | 6856 | 7687.6 | 2 | 2 |
| Paez et. al [28] | NS | Count | NS | 0+ | 24(MM2+)/13(MM3+) | 48.5 | yes | yes | no | 1844 | 2306.0 | 16 | 4 |
| Glynn et. al [13] | MM2+ | Count | 147 | 50+ | 66.2 | 82.5 | yes | no | no | 2211 | 2602.0 | 2 | 2 |
| Naessens et. al [29] | MM2+ | Count | 259 | 18-64 | 54.3 | 82.5 | yes | no | no | 13285 | 16245.0 | 4 | 4 |
| Nagl et. al [35] | MM2+ | CIRS | 33 | 65+ | 86.4 | 94.8 | yes | no | no | 3778 | 4422.0 | 2 | 2 |
| Carreras et. al [36] | NS | CRG model | all 857,385 ICD codes (815,227 diagnostics and 42,158 procedures) | 0+ | 17.8 | NA | yes | no | no | NA | NA | NA | NA |
| Kuo et. al [45] | NS | counting the number of Rx-MG | 55 | 0-71 | 80 | NA | yes | no | no | 1045 | NA | 4 | NA |
| Lochner et. al [30] | MM2+ | Count | 15 | 0+ | 67.3 | 92.6 | yes | no | no | 13949 | NA | 6 | NA |
| Machlin et. al [31] | MM2+ | Count | 20 | 18+ | 25.0 | 60.3 | yes | yes | no | 11934 | NA | 4 | NA |
| McRae et. al [41] | MM2+ | Count | 6 | 50+ | 55.8 | 81.0 | yes | yes | no | 1781 | 2014 | 2 | 2 |
| Heider et. al [37] | MM2+ | CIRS-G | 14 | 57-84 | NA | 74.0 | yes | yes | no | NA | NA | NA | NA |
| Orueta et. al [38] | MM2+ | ACG | 52 | 0+ | 23.6 | 63.6 | yes | no | no | NA | NA | NA | NA |
| Pati et. al [46] | MM2+ | Count | NS | 18+ | 1.3-30.6 | NA | yes | no | no | 240 | NA | NA | NA |
| Bahler et. al [39] | MM2+ | Count | 22 | 65+ | 76.6 | 94.7 | yes | no | no | 8233 | NA | 5 | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | 1.4% in 18–29 years old to 40.0% in those aged 70+ years | NA | yes | yes | no | 655 | NA | NA | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | | NA | yes | yes | no | 92 | NA | NA | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | | NA | yes | yes | no | 165 | NA | NA | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | | NA | yes | yes | no | 151 | NA | NA | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | | NA | yes | yes | no | 49 | NA | NA | NA |
| Lee et. al [40] | MM2+ | Count | 9 | 18+ | | NA | yes | yes | no | 60 | NA | NA | NA |
| Meraya et. al [32] | MM2+ | Count | 4 | 21+ | 100.0 | NA | yes | yes | no | 12317 | 16454 | NA | NA |
| Picco et. al [44] | MM2+ | Count | 10 | 60+ | 51.5 | 80.7 | yes | yes | no | 11167 | NA | 2 | NA |
| Carpenter et. al [42] | NS | Count | 11 | 50+ | 71.1 | 3.4 | yes | yes | no | 4447 | 3415 | 3 | 2 |
| Cohen et. al [43] | NS | Count | 9 organ systems | 0-16 | 6.7 | NA | yes | no | no | 36434 | NA | NA | NA |
| Ananth et. al [33] | NS | Count | 9 organ systems | 0-17 | 66.1 | 88.59 | yes | no | no | 252313 | 360046 | 4 | 4 |
| Zhong et. al [34] | NS | Count | 20 | 1-19 | 17 | 44.84 | yes | no | no | 8551 | 15797 | 4 | 6 |

*All costs are in $ (1 EUR=1.0886 USD;1 AUD=0.762966 USD;1 INR=0.014948 USD;1 CHF=1.005635 USD;1 CNY=0.143719 USD;1 MXN=0.049118 USD;1 RUB=0.016234 USD;1 ZAR=0.071561 USD;1 SGD=0.717926 USD; December 18, 2016). ACG, Adjusted Clinical Groups; Rx-MG, Rx-defined morbidity groups; CRG, Clinical Risk Groups; CIRS, Cumulative Illness Rating Scale; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; ICD, the International Classification of Diseases; MM, multimorbidity; MM2+, two-cutoff count method of multimorbidity; MM3+, three-cutoff count method of multimorbidity; y.o., years old; NS, not specific; NA, not available.

**Table 6-3.** Answers to the methodological questions by study.

| Questions/answers | All studies | Hwang et. al [23] | Garis et. al [24] | Wolff et. al [3] | Anderson et. al [25] | Thorpe et. al [26] | Schoenberg et. al [27] | Paez et. al [28] | Glynn et. al [13] | Naessens et. al [29] | Nagl et. al [35] | Carreras et. al [36] | Kuo et. al [45] | Lochner et. al [30] | Machlin et. al [31] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1 Was a clear definition of the illness given?** | | 1 | p | p | 0 | p | p | 0 | 1 | 1 | 1 | p | p | 1 | 1 |
| **2 Were epidemiological sources carefully described?** | | 1 | 1 | 1 | P | 0 | 1 | 1 | 1 | 0 | 1 | p | 1 | 1 | 1 |
| **3 Were direct/indirect costs sufficiently disaggregated?** | | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| **4 Were activity data sources carefully described?** | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | p | p | 1 | 1 | p |
| **5 Were activity data appropriately assessed?** | | 1 | 1 | 1 | 0 | p | 1 | 1 | 1 | p | 1 | 1 | 1 | 1 | p |
| **6 Were the sources of all cost values analytically described?** | | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | p | 0 |
| **7 Were unit costs appropriately valued?** | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | p | 1 | 1 | 1 |
| **8 Were the methods adopted carefully explained?** | | p | 1 | 1 | p | p | 1 | 1 | 1 | 0 | 1 | 1 | 1 | p | p |
| **9 Were the major assumptions tested in a sensitivity analysis?** | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **10 Was the presentation of study results consistent with the methodology of the study?** | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Total score by study** | | | | | | | | | | | | | | | |
| **YES(1)** | 165 | 8 | 6 | 6 | 3 | 4 | 7 | 8 | 9 | 3 | 8 | 4 | 7 | 6 | 4 |
| **NO(0)** | 58 | 1 | 3 | 3 | 5 | 3 | 2 | 2 | 1 | 6 | 1 | 2 | 2 | 2 | 3 |
| **PARTIALLY(p)** | 37 | 1 | 1 | 1 | 2 | 3 | 1 | 0 | 0 | 1 | 1 | 4 | 1 | 2 | 3 |

**Table 6-3. (Continuous)**

| Questions/answers | All studies | McRae et. al [41] | Heider et. al [37] | Orueta et. al [38] | Pati et. al [46] | Bahler et. al [39] | Lee et. al [40] | Meraya et. al [32] | Picco et. al [44] | Carpenter et. al [42] | Cohen et. al [43] | Ananth et. al [33] | Zhong et. al [34] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1 Was a clear definition of the illness given?** | | 1 | 1 | 1 | p | 1 | 1 | 1 | 1 | p | p | p | p |
| **2 Were epidemiological sources carefully described?** | | 1 | 1 | 1 | 1 | 1 | p | 1 | 1 | 1 | 1 | 1 | 1 |
| **3 Were direct/indirect costs sufficiently disaggregated?** | | 0 | p | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 |
| **4 Were activity data sources carefully described?** | | 1 | 1 | 1 | 1 | 1 | 1 | p | p | 1 | 1 | 1 | p |
| **5 Were activity data appropriately assessed?** | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | p |
| **6 Were the sources of all cost values analytically described?** | | 1 | p | 1 | p | 1 | 1 | 0 | 1 | 1 | p | 1 | 1 |
| **7 Were unit costs appropriately valued?** | | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **8 Were the methods adopted carefully explained?** | | 1 | 1 | p | 1 | 1 | p | 1 | 1 | 1 | 1 | 1 | 1 |
| **9 Were the major assumptions tested in a sensitivity analysis?** | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **10 Was the presentation of study results consistent with the methodology of the study?** | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Total score by study** | | | | | | | | | | | | | |
| **YES(1)** | 165 | 8 | 7 | 8 | 6 | 8 | 6 | 5 | 8 | 8 | 6 | 7 | 5 |
| **NO(0)** | 58 | 2 | 1 | 1 | 2 | 2 | 2 | 4 | 1 | 1 | 2 | 2 | 2 |
| **PARTIALLY(p)** | 37 | 0 | 2 | 1 | 2 | 0 | 2 | 1 | 1 | 1 | 2 | 1 | 3 |

Total score by study is the sum of answers. P, partially.

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# Chapter 7. Discussions

This chapter discusses the findings and implications of this thesis and places them in the context of the international literature. First, the methods are revisited, then the study findings are summarized, followed by a discussion of the implications of this research for the measurement and surveillance of multimorbidity, and, finally, recommendations for future research in this field are provided.

In addition, this thesis aimed to accomplish the following:

i. To explore the associations between multimorbidity and HRQoL [Chapter 3], HSU [Chapter 4], LPT [Chapter 5] and the related financial burden [Chapter 6], particularly in the Australian working population, and

ii. To determine whether the current large national prevalence surveys are adequately designed for the surveillance of multimorbidity [Chapter 3-5].

## 7.1 Recap of Methods

### 7.1.1 General recap

The data presented in this thesis were collected from three different sources. The data used in **Chapter 3** were derived from the NSMHWB-CURF 2007. The NSMHWB is a nationally representative household survey of 8,841 adults aged 18 to 65 years conducted by the ABS between August and December 2007. The ABS collected information on the presence of multiple chronic conditions based on Australian priority areas and on HRQoL using the AQoL instrument [1].

The data used in **Chapter 4** were derived from the 2011-13 nationally representative cross-sectional Australia NHS. The NHS was conducted by the ABS from March 2011 to March 2012 and collected information on the presence of multiple chronic conditions, health care service utilization for each chronic condition and employment

status. This information allowed us to assess the health care needs of a representative sample of the Australian working population within the context of multimorbidity.

The data used in **Chapter 5** were derived from the 2013 pH@W survey of a representative sample of state government employees in Tasmania (n=3,228). This sample represented a typical public sector workforce, albeit with a higher percentage of females than the general Australian workforce (71.7% and 45% [2], respectively). The pH@W survey aimed to determine the needs of TSS employees. Therefore, generalizing these findings to all working Australians or to other working populations, should be performed with caution.

Finally, the study presented in **Chapter 6** involved a systematic search of COI studies on multimorbidity published in English from 2000 to 2016. The inclusion criteria: peer-reviewed, cross-sectional, cohort and modelling COI studies on multimorbidity. Studies focused on an index disease were excluded. The data extracted for each eligible study included the definition, measure, and prevalence of multimorbidity, the number of included health conditions, age range of the sample, COI methodology, proportion of multimorbidity costs, and the average costs per capita. The adapted British Medical Journal Checklist was used to assess the study quality. Costs were converted to USD using the 2016 exchange rate for each currency, with adjustments over time based on the Consumer Price Index.

### 7.1.2 Definitions of multimorbidity

**Chapter 3** used count-based and cluster-based methods to identify multimorbidity using a pre-specified list of eight chronic conditions. In **Chapter 4**, multimorbidity was identified using a count-based method, using a cut-off value of "two chronic conditions" from a pre-specified list of eight chronic conditions; these conditions differed from those used in **Chapter 3.** The included conditions depended on the information collected in the surveys. In **Chapter 5**, multimorbidity was identified using a count-based method with a "two chronic conditions" cut-off value based on a pre-specified list of twenty chronic conditions. As no unique definition of multimorbidity exists, including the different definitions and measures in a systematic review was necessary and appropriate. Therefore, **Chapter 6** did not specify the

definition of multimorbidity but summarized the costs of multimorbidity in terms of the definitions.

## 7.2 Key findings

### 7.2.1 Effect of multimorbidity definition on HRQoL

The study reported in **Chapter 3** is the first, to our knowledge, to compare number-based and cluster-based definitions of multimorbidity using nationally representative data. This was achieved by determining the associations of multimorbidity with HRQoL, an important population health indicator. Based on a head-to-head comparison of a count and an alternative statistical approach to defining multimorbidity, this result is consistent with previous studies and validated the use of a hierarchical clustering approach when the outcome of interest is HRQoL. Moreover, this work established that a simple count fails to identify whether specific conditions of interest drove the occurrence of poorer HRQoL. Researchers should exercise caution when selecting a definition of multimorbidity as it may significantly influence the observed association with study outcomes. These findings advanced the literature by assessing the underlying driver of health status (multimorbidity) at the methodological level and confirmed that multimorbidity is a problem in the Australian general population. Prior to this epidemiological analysis with a head-to-head comparison of health outcomes, the impact of multimorbidity in Australia was not well documented, particularly at the population level.

The count-based method does not account for the type of chronic conditions present, and thus this method can determine the overall influence of multimorbidity on HRQoL but not the specific disease contributes to the associated HRQoL. The cluster-based method, hierarchical clustering in particular, could capture the common clusters; a finding supported by sensitivity analysis, including factor analysis, principal component analysis and K-means clustering. Combining these findings validated the hierarchical clustering approach and proved it more useful and informative when HRQoL is the outcome of interest. However, future research is warranted to clearly describe the adopted definition of multimorbidity.

### 7.2.2 Associations between multimorbidity and HSU for arthritis and CVD

After discussing multimorbidity in the general population, this thesis proceeded to address it in the Australian working population, which is a relatively healthier population and is central to the economic well-being of the country. To our knowledge, the study described in **Chapter 4** is the first to examine the associations between multimorbidity and disease-specific healthcare service utilization in the workforce. Multimorbidity is known to increase the overall healthcare service utilization in the primary healthcare setting and in the general population, particularly in the elderly. However, in contrast to the existing studies, this study revealed multimorbidity also increased healthcare use in the working population, but single disease-specific healthcare use was not always positively associated with the existence of multimorbidity. Arthritis and CVD were the health conditions in the Australian workforce that showed higher healthcare utilization when comorbid with other chronic health conditions. This finding may inform future longitudinal research into when a higher burden of multimorbidity on HSU emerges for different combinations of disorders. These findings can also inform workforce health promotion interventions, and future research could focus on multimorbid employees living with arthritis or cardiovascular disease. Moreover, reforming health systems or policies to properly address these two health conditions may be beneficial, at least when focusing on the workforce.

### 7.2.3 Associations between multimorbidity and absenteeism, presenteeism and total LPT

In **Chapter 5**, this thesis explored the work attendance and productivity consequences of multimorbidity in the workforce. The definition of LPT has differed between the productivity measures used in the literature including absenteeism, presenteeism and total LPT, which is considered the sum of absenteeism and presenteeism. This study obtained all three estimates from employees' self-reported data over a 28-day period, consistent with common measurements of LPT in the health field. The results showed a strong, positive association between the presence of multimorbidity and LPT. Additionally, having more chronic conditions was associated with greater LPT. These findings were consistent with prior evidence and suggest the management of single

health conditions in order to reduce health-related LPT may not, in fact, be tackling one of the strongest correlates of LPT- multimorbidity. Moreover, significant differences in LPT between men and women reporting multimorbidity were also identified. The female employees in in this public sector sample were more likely to report higher LPT when facing chronic conditions compared to their female counterparts without chronic condition, while for male employees an association with LPT was not observed until four or more chronic conditions were reported.

### 7.2.4 A systematic review of COI studies on multimorbidity

The systematic review outlined in **Chapter 6** was the first known attempt to compile information on the economic burden of multimorbidity. It is difficult to compare results across studies when the "disease" of interest is multimorbidity because the included studies differ in their definition and measurement of multimorbidity, the health conditions included, and the samples and economic estimates used. Therefore, the discussion was limited to describing the results but not pooling them.

The main contribution of this review is the accumulation and summary of the available evidence on the costs of multimorbidity based on COI studies with standardized and acceptable methodologies and how the different methodologies were used. Further examination of the definition resulted in two opposite outcomes: exploring "multimorbidity" was not only with the count-methods even it was the most popular approach in COI studies, on the one hand, and reducing the comparisons between studies exactly due to different definitions of multimorbidity, on the other. This simple but important finding revealed multimorbidity cannot be managed without a clearer framework or better understanding of its definition.

This study also found the methodology used to derive costs differed markedly between studies. The average annual costs per patient with multimorbidity ranged from $49-$252,313. Using a cut-off of two or more conditions, the proportional increase in cost for multimorbid compared to non-multimorbid ranged from 100% to 1500% in the 17 available studies. The highest costs ($252,313) were found in a study of children in the US [3]. Using a cut-off of three or more conditions, the average costs were 2-10 times the costs of those without multimorbidity in 12 studies. In the 10

studies providing a breakdown of costs, the largest proportion of costs was spent on inpatient care or prescriptions in studies with a non-societal perspective, whereas the largest proportion was on social care costs in studies from a societal perspective [4]. These findings revealed that COI studies on multimorbidity are highly heterogeneous and that multimorbidity has been associated with a considerable economic burden. Referring to other COI reviews, the included studies were identified with good quality if the score was 7 and over (out of 10). Thirteen studies met this requirement and of them, only one study was with the best quality and scored 9. There were three studies conducted of children, with such studies rare due to the very low prevalence of multimorbidity amongst this age group. Those "extremely young" samples in multimorbidity were threatened by serious chronic conditions and some even died during the study, however, the results also showed the high costs for them in the following years, which was consistent with the findings from the other included studies.

## 7.3 Implications of findings

These findings have important implications for "multimorbidity" regarding HRQoL, HSU, LPT and the financial burdens, particularly in the working population. These studies were conducted with samples of the Australian population. However, as multimorbidity is now a common global health concern, the findings of this thesis may be relevant to "multimorbidity" settings at a fundamental level and could inform future research to address the identified gaps and shape health care systems. That said, all the studies presented in this thesis were cross-sectional, and thus no conclusions can be drawn regarding causality.

The first implication of the results is **theoretical**. The study in **Chapter 3** aimed to examine the performance of count-based and cluster-based definitions of multimorbidity regarding sociodemographic profiles and HRQoL in a general population. At the methodological level, multimorbidity does not have a single definition. Whilst there is a very general definition, i.e., "individuals who have two or more co-occurring chronic health conditions", it does not allow for identification of multiple morbidity. For example, it does not specify whether the multiple conditions exist separately or could be causally linked. Therefore, without an index disease

'multimorbidity' could not appropriately address causally linked conditions while 'comorbidity' could. Accordingly, this study performed head-to-head comparisons of definitions and confirmed the existence of an inverse relationship between multimorbidity and HRQoL in the Australian population. The analyses validated the hierarchical clustering approach when the outcome of interest was HRQoL, and found a simple count failed to identify whether there are specific combinations of interest driving poorer HRQoL. This finding suggests providing targeted health services to multimorbid individuals reporting only certain combinations, such as CVD and arthritis or MDD and anxiety disorder, may improve their HRQoL [5].

However, the count method may still be useful to some extent because it is generally easy to estimate the number of conditions using many of the currently available datasets. Hierarchical clustering could be used as a supplementary tool in population or large administrative datasets to capture specific common clusters of multimorbidity. Regardless of which definition was adopted, an inverse association of multimorbidity with HRQoL was observed. This finding indicates multimorbidity is a problem in the Australian general population and a standard definition is needed.

The second implication of the findings is **practical in nature**. The research to date has explored the consequences and quality of healthcare for multimorbidity in select population settings, including the primary healthcare and the elderly [6]. This thesis initially focused on a non-selected population as the existing research indicates more people in the general/working population are living with multimorbidity without receiving appropriate treatment. For example, multimorbid individuals often receive conflicting medical advice for the different health conditions they are living with, or duplicate prescriptions from the different specialists [7, 8]. Further, multimorbid individuals are sometimes advised to take prescription medications for different health conditions, by different specialists that have potentially harmful interactions without an understanding of the consequences [9, 10].

Even with a certain working population, the findings of multimorbidity and LPT could help employers realize the value of maintaining a healthy working population, and can be considered by employers as they develop health benefits and preventive health care intervention strategies. While the severity of the increasing prevalence of

multimorbidity has been recognized, little is known about how to reduce the challenges in practice, due to a lack of knowledge about multimorbidity in the broader population rather than only in the older population or primary health care.

This thesis provides new insights into the need for preventive strategies and improved treatment of people living with multimorbidity, which will become more and more important not only because of the global aging populations but also the aging workforces. There are care planning items for chronic disease that mainly focuses on the management of a single disease or the index disease and hence are insufficient for multimorbidity. And the primary care service which largely costs Australian financing system a lot is not very helpful for multimorbidity. The results of the currently available data highlight the need for future data collection and could also be helpful to aid in the design of a better functioning and financed health system for these people living with multimorbidity.

Finally, the third implication of this relates to the global challenge of multimorbidity facing the health care field. Some international institutes, such as the NICE, the Academy of Medical Sciences, and the International Research Community on Multimorbidity (IRCMo), have started to improve access to existing knowledge, develop evidence-based strategies and facilitate international collaboration in research on multimorbidity. Of these institutes, the IRCMo has called for evidence to establish a consistent definition of multimorbidity to encourage an improved understanding of multimorbidity. NICE is more focused on developing relevant guidelines not only for clinical assessment and management but also for the working populations. This thesis highlights the fact that the currently available data in Australia restrict further exploration of multimorbidity.

As a part of this thesis, it was originally planned to estimate the lifetime societal costs of multimorbidity in the Australian working population among workers who had two or more prevalent chronic conditions. That study planned to use cohort simulation and state-transition models to simulate the movement of a hypothetical cohort of the working population between health states over a lifetime according to the probabilities derived from a quality epidemiological data source and the existing literature [11]. However, it was deemed unfeasible due to a lack of requisite inputs

related to the costs of multimorbidity. The AIHW confirmed that the national health care statistics were not currently collated in a format amenable to a study of this type. This valuable experience helped us rethink the methods of data collection to embrace the heterogeneity of multimorbidity. Therefore, future research on multimorbidity is warranted and should use research-friendly surveys, which allow the researchers access multimorbidity via various approaches within one dataset.

## 7.4 Limitations

Despite the strength of the studies conducted in this thesis and the aforementioned implications regarding HRQoL, health care service use, productivity loss and the related financial burdens, particularly in the working population, the limitations must also be considered. For example, the analyses conducted in this thesis were restricted to self-reported information. Further, the data source used did not link to medical records. Therefore, the results may be under- or over-estimates due to recall bias. For example, conditions such as mental disorders, are likely under-reported due to stigma, and behavioural disorders or diabetes often present as "silent" conditions, which could not be recognised by patients [12]. That said, the samples used in this thesis were large. For example, the NSMHWB2007 included approximately 8,800 Australians, the NHS 2011-12 included 20,250 Australians, and even the state-level data pH@W 2013 included more than 3,000 Australian employees. The validity of self-reported chronic conditions has been indicated in different contexts [13-17]. Moreover, self-reported data are cost-effective and convenient for gathering information in population-based surveys [18]. These studies also progressed beyond the typical samples used in multimorbidity studies, which are often restricted to older or clinical populations.

This thesis did not account for the severity of health conditions, which could prove useful in clinical settings [19, 20]. However, national prevalence surveys of community-dwelling populations tend to use a simple count method, rather than comorbidity measures, which weight conditions by their severity [21]. There are two reasons for this: i) the weights of functional disease burden change by disease coding systems, and thus the scoring algorithms used to generate weights need regularly updating; and ii) the considerable costs of non-count methods are generally not feasible when conducting a national prevalence survey due to the additional respondent burden. A

further limitation is that the studies in **Chapters 3, 4 and 5** excluded acute conditions [6]. Including more health conditions is more likely to provide a more comprehensive understanding of an individual's health status, however, acute conditions were not considered in this thesis, because of the high probability of their temporarily impact on health status only [22] and therefore irrelevant to long-term health care planning.

In addition to the shared limitations of the studies, each study has its own specific limitations. In Chapter 3, the data used were derived from a survey focused on mental health and well-being. So the assessments of chronic physical conditions were relatively brief, although consistent with many population prevalence surveys [23]. In Chapter 4, the GP visits may be underestimated because some chronic health conditions are not serious and could be self-managed on a daily basis by patients themselves without any health care visits, especially in just a short period of one year. In Chapter 5, the survey used did not limit the measurement of productivity loss to the pre-specified health conditions. Therefore, employees may have reported on LPT due to other health problems. Hence, the impact of multimorbidity on productivity loss may have been underestimated. Further, recall bias may have been introduced as the rate of productivity loss was captured through the employees' self-reported responses. However, the employees are in a better position than researchers to recognize, evaluate and rate their overall work performance based on self-reported evaluation. Moreover, previous research has shown that employees' self-reported days lost are consistent with employers' reported days lost [24].

Another limitation worthy of note is that, this study obtained cross-sectional data in 2013. Therefore, the direction of causality cannot be explored, and the results may only reflect short-term (four-week) employee behaviour, and the associations of multimorbidity with that behaviour. This methodology reduced the potential for recall bias of the self-reported questionnaire [25], as employees' absenteeism or presenteeism behaviour may change over time. For example, based on our study, men may not currently be willing to take days off, but they may be more willing to do so at a later time, and after several years, they may ask for even more days off. However, this claim cannot be proven with cross-sectional data and requires further investigation using longitudinal data. For this reason, we presented the results as they were, in

contrast to one study, which annualized the same duration measures to reflect an entire work year [26].

It is critical to note the increasing length of recall time may reduce the accuracy of estimation of the impact of health problems on their productivity by respondents themselves [25]. However, if the focus of survey is on the frequency of productivity loss due to illness, the potential bias may be reduced [27]. Finally, unlike the pathway to estimating the lost work time which did not distinguish the different types of lost time, the used pathway in Chapter 5 did not account for workers coming in early or leaving late on other days. Additionally, we surveyed a sample of TSS employees un-representative of the total workforce. Moreover, pH@W used a self-report, short and simple measure to identify health conditions, which was commonly used in large population health surveys such as NHS [28] and NSMHWB [23].

In Chapter 6, the results of this review were limited by the nature of the studies identified. The main limitation of this review was its inability to include all relevant studies. Costs were estimated in 16 countries or regions from 1996 to 2013. The large number of abstracts derived from the databases improved the sensitivity of our search strategy. The absence of a MeSH term for multimorbidity was a clear limitation. There was no published checklist for the quality of COI studies. Therefore, we adopted the modified British Medical Journal Checklist for authors and peer reviewers of economic submissions [29], which could help the BMJ editors improve the efficiency of the editorial process [30]. The limitation of its scoring method was lack of weighting. Therefore, there was possible the scores were more likely affected by some items than others. Further works must be performed in these areas. However, adding multimorbidity-related terms from previous studies to our search strategy helped mitigate this limitation. We included papers published in English only, which restricted our sample.

Moreover, the utility of COI studies in aiding policy decision making has been debated, [31, 32] and its inability to prioritize resources has been criticized [33, 34]. COI studies serve a different purpose than health economic evaluations (e.g., cost-benefit, cost-effectiveness, and cost-utility analyses), which aim to describe the economic burden of a health condition on society which could potentially be avoided if the

condition is eradicated [35-37]. COI studies can provide useful information as long as they adhere to standardized and acceptable methodologies [38, 39]. Furthermore, the results of COI studies have been used by organizations such as the World Bank and the World Health Organization to estimate public, private and total national health expenditure on a global scale [40]. Different stakeholders can utilize COI studies for different purposes [41]. For example, for resource allocation purposes, governments may obtain the financial impact of a health condition on public budgets; whereas pharmaceutical companies are more interested in health condition with high management and direct research costs [41]. However, caution is warranted when using COI studies. COI studies should be adopted in combination with other thorough economic evaluations in order to get optimal resource allocation [42].

## 7.5 Recommendations for future research

This thesis has provided evidence that multimorbidity is a common issue facing the Australian population and indicated that the relevant healthcare policies and systems should be modified accordingly. Specifically, research using multimorbidity-specific survey data is needed within the context of the current Australian healthcare framework to investigate the multi-directional multimorbidity and to support the development and refinement of current guidelines.

Further, to improve the effectiveness and credibility of care management, research examining the overall health status of the general population living with multimorbidity, particularly studies using HRQoL to present health status, should include clusters of multiple health conditions, which could be captured by adding hierarchical clustering.

Finally, data on the health service utilization of patients with multimorbidity, collected using a national representative sample, is required to identify comprehensive healthcare utility patterns rather than single chronic conditions, in order to better organize the limited health resources and optimize the input-output rate. Further, using a representative sample of the Tasmanian state service workforce, this thesis establishes that multimorbidity plays an important role affecting the productivity of employees, and hence suggests, support in the management of multimorbidity, and

that the Australian health system could and need to be improved. Because the indirect health costs are likely to be greater than the direct health costs and the population of multimorbid working adults are continuously growing. This also identified gender differences in multimorbidity-related lost productive time which should be considered in health planning for employees living with multimorbidity and how we organise the health system to support people with multimorbidity. Specifically, compared to their counterparts without any chronic conditions, female employees begin to report productivity loss when they have one chronic condition, whereas male employees are more likely to report productivity loss when living with four or more chronic conditions. However, the sample used is not representative of all Australian working population, meaning further research is required using a representative sample of Australian employees to investigate the potential association of work productivity loss with multimorbidity, and the impact of gender on this relationship.

Further research is also needed to establish an approved list of health conditions which contribute to multimorbidity in different settings, which take into account local context, and regional differences. That said, regardless of which definition of multimorbidity is used, the included health conditions need to be chronic because in order to inform long-term health planning, and must also include the main four global chronic health conditions, cardiovascular diseases, cancers, chronic respiratory diseases and diabetes [43]. An accessible, internationally recognised definition of multimorbidity is necessary to ensure global comparisons over time. Innovations in health system delivery for people with multimorbidity are being trialled in various settings. For example, nurse navigators or coordinators have been introduced to the health system in the state of Queensland to meet the complex needs of patients and help them "navigate" the healthcare system. Since 2015 an additional 400 experienced nurses have been progressively added to the state's Hospital and Health Services over the next 4 years [44, 45]. When facing the increasing population with multimorbidity, the efficacy of this service innovation is not yet known. This thesis indicated the specific groups with the relatively higher needs than others. Future research could be more focused on these groups.

## 7.6 Summary and Conclusions

In conclusion, this thesis confirmed that multimorbidity is a significant public health problem in the general population, as well as in the workforce, and addressed three important gaps in the current understanding of multimorbidity.

- The Theoretical Gap. Comparison of definitions identified the count method is still useful given its ease of calculation, but consensus is needed on whether a 2-disorder or 3-disorder cut-off is most useful. Hierarchical clustering could be used as a supplementary tool to capture specific common clusters of multimorbidity. Most importantly, a uniform definition of multimorbidity is needed.
- The Practical Gap. This thesis quantified the impact of multimorbidity on health care resource consumption in the Australian workforce and on productivity in a large Australian occupational cohort. The heavy economic burden of multimorbidity as demonstrated in the systematic review suggests that multimorbidity will be increasingly important in the future, especially considering the social changes related to delayed retirement. Moreover, this thesis has also shown and highlighted the tremendous financial implications for health care service design and delivery for meeting the needs of people living with multimorbidity.
- The Methodological Gap. Results highlighted that currently available data restrict further explorations of multimorbidity. Standardization of the chronic disease surveillance methodologies used in national prevalence surveys would facilitate the epidemiological investigation of multimorbidity in the general population. Recommendations have been provided to improve the assessment and surveillance methods of multimorbidity at the population level.

## 7.7 References


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